Nederlandse Ziekenhuisfarmaciedagen, 7 en 8 november 2019

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POPULATION PHARMACOKINETICS OF VANCOMYCIN IN OBESITY: FINDING THE OPTIMAL DOSE FOR (MORBIDLY) OBESE INDIVIDUALS

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Background

For vancomycin treatment in (morbidly) obese patients, there is no consensus on the optimal dose that will lead to the pharmacodynamic target (AUC_{24h} = 400-700 mg * h/L). This prospective rich sampling study was designed to quantify the pharmacokinetics of vancomycin in morbidly obese and non-obese individuals, ultimately to design an optimal dosing strategy to guide vancomycin dosing in the obese.

Methods

Morbidly obese individuals (n = 20, median [range] total body weight (TBW) 139 kg [111-235 kg]) undergoing bariatric surgery and non-obese healthy volunteers (n = 8, TBW = 69.5 kg [60-85 kg]) received a single vancomycin dose (obese: 12.5 mg/kg, maximized at 2500 mg; non-obese: 1000 mg) with plasma concentrations measured over 48 hours (11-13 samples per individual). All individuals had a normal renal function (estimated GFR > 60 mL/min). Modelling and simulations were performed using NONMEM7.4. External validation of the model was done by visual predictive check and calculation of the median prediction error (criterion: < 20%) and root mean squared error (criterion: < 5 mg/L), using previously published data [1]. With the final model, different dose regimens were evaluated using Monte Carlo simulations in 10.000 virtual subjects with body weights ranging 60-230 kg.

Results

In a three-compartment model, clearance was found to increase with TBW (P < 0.001) according to the equation CL (L/h) = 5.72 [95% CI = 5.34-6.1] * $(TBW/70)^{0.535\ [95\%\ CI\ =\ 0.36\text{-}0.67]}$. Peripheral volume of distribution increased linearly with TBW (P < 0.001). The model predicted the concentrations of obese individuals in the external dataset without bias and with good precision. Simulations showed that a dose of 35 mg/kg per day (maximum 5500 mg/day) resulted in a > 90% target attainment (AUC > 400 mg * h/L) in individuals up to 200 kg. Within-target trough concentrations were 5.7-14.6 mg/L (twice daily dosing). For obese individuals receiving continuous infusion, a loading dose of 1500 mg is required to reach steady-state on day one.

Conclusion

In this prospective, rich sampling study, vancomycin pharmacokinetics were quantified with clearance being related to TBW in non-obese and morbidly obese individuals. We recommend that vancomycin should be dosed as 35 mg/kg per day (maximized at 5500 mg/day) in (morbidly) obese patients without renal impairment. When given over two daily doses, trough concentrations between 5.7 and 14.6 mg/L are sufficient to reach the target exposure of 400 – 700 mg*h/L in obese individuals. Future research should focus on evaluation of this model in morbidly obese patients with renal insufficiency.

THE IMPACT AND EXTENT OF RENAL FUNCTION ON THE CLEARANCE OF CIPROFLOXACIN IN ICU PATIENTS USING DIFFERENT MARKERS FOR RENAL FUNCTION

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Background

Currently ciprofloxacin dosing is adjusted based on renal function. Yet, the impact of renal function on the clearance of ciprofloxacin is largely unknown including which estimation of glomerular filtration rate best predicts ciprofloxacine clearance. We set out to explore how renal function correlates with ciprofloxacin clearance and we hypothesized that eGFR estimated using both serum creatinine (sCr) and serum cystatin C (sCysC) provides better prediction of ciprofloxacin pharmacokinetics in critically ill (ICU) patients than eGRF estimation on sCR alone.

Methods

In this observational multi-center study, adult ICU patients receiving ciprofloxacin were eligible for inclusion. Patients on renal replacement therapy were excluded. Dose and duration of therapy were determined by the patient's physician. Within 24 hours of initiation of ciprofloxacin, a pharmacokinetic (PK) curve was drawn at 8 different timepoints and sCR, sCysC and urinary creatinine were collected. Linear regression was performed to determine relations between log-transformed pharmacokinetic parameters $AUC_{0\text{-}24}$ and clearance (CL) and MDRD, $CKD\text{-}EPI_{creat}$, $CKD\text{-}EPI_{cys}$, $CKD\text{-}EPI_{creat\text{-}cys}$ and 24-hour urine creatinine clearance.

Results

Thirty-seven patients (17 female) were evaluable, median (range) age 68 (30-87) years, sCr 88 (43-257) µmol/L and sCysC 1.42 (0.66-3.58) mg/L. PK sampling resulted in a median dose corrected $AUC_{0\text{-}24}$ of 30.35 mg·h/L (range = 14.46-103.48 mg * h/L), median through concentration of 0.56 mg/L (range = 0.13-3.26 mg/L), median maximum concentration of 3.15 mg/L (range = 1.15-7.35 mg/L) and a median CL of 26.35 L/h (range = 7.73-55.32 L/h).
Measured urinary creatinine clearance and different equations of eGFR are significantly ($P < 0.5$) correlated with AUC with Rsquare of: MDRD 0.4933, $CKD\text{-}EPI_{creat}$ 0.4815, $CKD\text{-}EPI_{cys}$ 0.3744, $CKD\text{-}EPI_{creat\text{-}cys}$ 0.4495 and 24-hour urine creatinine clearance 0.4584. $CKD\text{-}EPI_{creat\text{-}cys}$ based on serum creatinine and cystatin C did not proof to correlate better to ciprofloxacin $AUC_{0\text{-}24}$ than estimations of eGFR using serum creatinine alone.

Conclusion

Renal function markers are a poor predictors of ciprofloxacin clearance. In addition, estimating eGFR using combined filtration markers, serum cystatin C and creatinine, did not provide better prediction of ciprofloxacin pharmacokinetics than eGRF estimation on serum creatinine alone. None of the ICU patients attained sufficient exposure to treat pathogens with an MIC of 1 mg/L and above ($AUC_{0\text{-}24}$/MIC > 125 mg * h/L).

INCIDENCE AND TIME-DEPENDENCE OF SUBTHERAPEUTIC AND SUPRATHERAPEUTIC VANCOMYCIN LEVELS IN CRITICALLY ILL PATIENTS: A RETROSPECTIVE STUDY

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Background

Timely and adequate antibiotic treatment is paramount in critically ill patients with a severe infection. In case of suspected or proven infection with Gram-positive bacteria, vancomycin is often the appropriate first line treatment. Since 2011 our protocol is to use continuous vancomycin infusion with therapeutic drug monitoring (TDM) with daily or less frequent measurements. We evaluated how effective our policy was in achieving the desired concentrations, i.e. 20 to 25 mg/L.

Methods

Retrospective analysis of vancomycin levels in adult patients admitted to our intensive care unit (ICU) over a 64 month interval who were treated with a vancomycin bolus followed by continuous infusion. Patients with only a single vancomycin level or receiving renal replacement therapy were excluded. Levels were classified compared with the desired range of 20 to 25 mg/L. Only vancomycin levels determined within 30 days of ICU admission were included.

Results

We included 354 patients with a total of 2148 vancomycin levels. The mean age ± SD was 58 ± 14, 61% were male and the acute physiology and chronic health evaluation score (APACHE-IV) was 76 ± 30 with a hospital mortality of 33%. The mean number of vancomycin measurements was 5.4 ± 5.8. Per patient the percentage of vancomycin levels < 15, < 20, within range, > 25 and > 30 mg/L was 22%, 43%, 26%, 31% and 12% respectively. The percentage of within range levels did not differ between survivors and non-survivors, although non-survivors had a higher fraction of levels > 25mg/L (< 0.001). Moreover, subtherapeutic levels decreased during therapy, while supratherapeutic levels increased. Remarkably, at two days after ICU-admission still only one out of three patients had vancomycin levels within the desired range.

Conclusion

Timely target attainment vancomycin is difficult with our current TDM-protocol. Protocol changes or more frequent vancomycin sampling appear to be mandatory.

INTEGRATION OF PLACENTAL TRANSFER IN A PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL TO CHARACTERIZE PARACETAMOL EXPOSURE AND METABOLIC CLEARANCE IN THE FETUS FOLLOWING MATERNAL INTAKE

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Background

Although paracetamol is frequently used during pregnancy, little is known about fetal paracetamol pharmacokinetics (PK) after therapeutic dosing. Research on paracetamol toxicity has focused on hepatotoxicity. Other adverse events (e.g. closure/constriction of fetal ductus arteriosus) might also be relevant and not only related to paracetamol exposure, but could also be related to exposure to its metabolites. Adequate models to predict fetal PK profiles and drug exposure are lacking. Physiologically based pharmacokinetic (PBPK) modeling can be a valuable tool. This study has two objectives. First, to develop a fetal-maternal (f-m) PBPK model that quantitatively predicts placental transfer and paracetamol exposure in the term fetus. Secondly, to quantify contributions of specific metabolic clearance pathways to total clearance in the term fetus.

Methods

An earlier established pregnancy PBPK model for prediction of maternal PK of paracetamol and its metabolites was structurally extended with a compartment representing fetal liver and integrated maturation of relevant enzymes (uridine 5'diphospho-glucuronyltransferase (UGT) 1A1, sulfotransferase (SULT) 1A1/1A3 and cytochrome P-450 (CYP) 2E1). To parameterize the model, placental transfer parameters were determined with ex-vivo human cotyledon perfusion experiments. Predicted maternal and fetal paracetamol PK profiles were compared with observed data from the umbilical cord. In addition, paracetamol concentration in the arterial umbilical cord was predicted for possible constriction/closure of ductus arteriosus.

Results

Paracetamol exposure in maternal venous blood was similar to that in fetal venous umbilical cord blood. The predicted paracetamol concentration in the arterial umbilical cord is 3.6 mg/L. Prediction of paracetamol clearance in the fetus indicated that the specific clearance to paracetamol-sulphate and N-acetyl-p-benzoquinonimine (NAPQI) were 0.8% and 0.06%, respectively.

Conclusion

Prediction of the specific clearance of paracetamol to its metabolites in the term fetus was quantified for the first time. Additionally, predicted paracetamol concentration in the arterial umbilical cord blood, suspected to be involved in ductus arteriosus constriction/closure, was below the suggested postnatal threshold (24.47 mg/L). However, incidental cases still occur. F-m PBPK models can constitute powerful tools to support informed decision-making in clinical setting when information from other sources is lacking or inconsistent.

ROLE OF DISEASE MODIFYING TREATMENT IN THE RISK OF ALLOIMMUNIZATION IN TRANSFUSED PATIENTS WITH MYELODYSPLASTIC SYNDROMES: A POPULATION-BASED STUDY

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Background

The majority of patients with myelodysplastic syndromes (MDS) require regular red blood cell (RBC) transfusions. Alloimmunization (AI) against blood products is an adverse event, causing time-consuming RBC compatibility testing. Current literature has not yet identified the influence of disease modifying treatment (DMT) on the risk of AI. Therefore, we performed this study to evaluate the effect of DMT on AI.

Methods

An observational, population-based study, using the HemoBase registry, was performed including all newly diagnosed MDS patients between 2005 and 2017 in Friesland, a province of the Netherlands. Information about transfusion dates, types, and treatment regimens was collected from the electronic health records and

laboratory systems. Blood products were matched for AB0 and RhD, and transfused per the 'type and screen' policy. After a positive antibody screening, antibody identification and Rh/K phenotyping was performed and subsequent blood products were (cross)matched accordingly. DMT was defined as hypomethylating agents, lenalidomide, chemotherapy and monoclonal antibodies. The effect of DMT was estimated with incidence rates, relative risks (RR) and hazard ratios (HR). Follow-up was limited to 24 months for cox regression analyses to avoid possible bias by survival differences. Statistical analyses were performed using IBM SPSS 24 and SAS 9.4.

Results

Out of 292 MDS patients, 236 patients received transfusions and were included in this study, covering 463 years of follow-up. AI occurred in 24 patients (10%). DMT was given to 67 patients (28%). Patients on DMT received more RBC transfusions than patients without DMT (median of 33 (range = 3-154) and 11 (range = 0-322) RBC units respectively, $P < 0.001$). Four AI events (6%) occurred in patients on DMT and 20 AI events (12%) occurred in patients without DMT. Cox regression analysis showed an HR of 0.30 (95% CI = 0.07-1.31, P = 0.11). The incidence rates per 100 person-years were 3.19 and 5.92 respectively. The corresponding RR was 0.54 (95% CI = 0.16-1.48, P = 0.26).

Conclusion

Based on our results, we conclude that the incidence of AI in an unselected, real world MDS population receiving RBC transfusions is 10%. Our data showed that patients on DMT received significantly more RBC transfusions but were less susceptible to AI. Therefore, extensive matching of blood products may not be necessary for patients on DMT. Larger studies are needed to confirm the protective effect of DMT on AI.

CISPLATIN, HOW SHOULD AND DO WE HYDRATE TO REDUCE NEPHROTOXICITY?

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Background

Nephrotoxicity is a frequently occurring and treatment-limiting side effect of cisplatin. To reduce the incidence and extent of nephrotoxicity, hydration is commonly applied. However, no clear evidence about the most optimal hydration is available and a large variety of hydration schemes seems to be applied. The aims of this study were to review the currently available evidence on hydration to prevent cisplatin-related nephrotoxicity and to obtain insight in the applied hydration schemes in the Netherlands.

Methods

Based on a literature search in Pubmed, relevant publications were summarized and compared with published guidelines. Furthermore, a survey was conducted amongst Dutch hospitals to obtain an overview of the applied hydration schemes in this country.

Results

The published studies mostly compared two or three hydration regimens. Often, more than one aspect of hydration differed between the treatment arms, e.g. volume of hydration and the addition of magnesium sulphate. Nevertheless, the studies predominantly indicate the benefit of hydration, mostly with sodium chloride 0.9%. Addition of magnesium sulphate also contributes to prevention of nephrotoxicity. The results about length and volume of hydration are inconclusive. In total, 41 hospitals responded to the survey including all 8 Dutch University Medical Centres, 17 teaching hospitals and 16 general hospitals. For the combination cisplatin-pemetrexed for non-small cell lung carcinoma, the hospitals showed a variety in multiple aspects of hydration. The prehydration volume varied from 1 to 2 litres administered over 60-1000 minutes. The posthydration volumes varied from 1 to 4 litres, infused in 120–1440 minutes. In addition, the composition of the hydration fluids differed between the hospitals: sodium chloride in various concentrations (0.45-2.9%), whether or not in combination with glucose and a variety of electrolytes and diuretics.

Conclusion

The current hydration guidelines and literature are inconclusive about the best hydration scheme. The survey amongst Dutch hospitals shows a large variation in hydra-

tion schemes applied in cisplatin treatment. The time required for a cycle of cisplatin treatment differs greatly between the hospitals which has consequences for the patient burden and hospital capacity. The results underline the need for evidence on hydration protocols and for harmonisation.

LONG TERM PEMETREXED-BASED CANCER TREATMENT LEADS TO NEPHROTOXICITY

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Background
Pemetrexed is widely used as an anti-folate cytostatic agent for the treatment of lung cancer. As it is primarily eliminated by renal excretion, adequate renal function is essential to prevent toxic exposure. Pemetrexed is currently contraindicated in patients with a creatinine clearance < 45 mL/min. Lung cancer patients are at risk of developing renal insufficiency due to use of nephrotoxic platinum-based drugs. However, growing evidence suggests that pemetrexed itself may also be nephrotoxic. Maintenance of adequate renal function is a requirement for safe, long-term pemetrexed treatment, either as monotherapy or combined with pembrolizumab. Therefore, the aim of this study was to describe the prevalence of nephrotoxicity and related clinical consequences during pemetrexed-based treatment. The secondary objective was to identify risk factors for the decrease in renal function.

Methods
For this retrospective cohort study, all patients who received at least one cycle of pemetrexed-based therapy between January 1st 2014 and February 1st 2019 at the Jeroen Bosch Hospital were identified. Patient demographics were collected, together with relevant information regarding comorbidities, comedication and cancer treatment. For assessment of renal function, serum creatinine measurements at baseline and end of therapy (maximum 28 days after last dose) were used to calculate the estimated glomerular filtration rate (eGFR) according to the CKD-EPI-formula. The primary outcome was the prevalence of a clinically relevant decline in eGFR (defined as ≥ 25% reduction) or cessation of therapy due to nephrotoxicity. For the secondary outcome, multivariate regression analysis with Bonferroni correction was performed to identify possible risk factors for the development of renal impairment during pemetrexed-based therapy.

Results
Of the 359 patients included in this analysis, 21% patients had a significant decline in renal function after treatment and 8.1% of patients discontinued treatment due to nephrotoxicity. Cumulative dose (≥ 10 cycles of pemetrexed based therapy) was identified as a risk factor for the primary outcome measure (adjusted OR = 5.66 (CI = 1.73-18.54)). There was a trend of increasing risk of nephrotoxicity with increasing number of comedications or comorbidities.

Conclusion
This study indicates the association between pemetrexed treatment and renal function decline and showed that the risk for renal function decline increases with the cumulative dose. Renal impairment is expected to become an even greater issue now that pemetrexed-based immunochemotherapy results in longer survival and thus longer treatment duration. Our data call for innovative interventions to maintain the safe and effective long-term treatment with pemetrexed.

DESIGN AND PRELIMINARY RESULTS OF A FEASIBILITY STUDY ON HOME-MONITORING GOUT FLARES WITH AN APP

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Background
Gout flares are considered a key outcome measure in gout treatment. Early treatment of gout flares increases patient well-being and warrants timely notification of the treating clinician. This study tests the usability, patient value and feasibility of a smartphone app (Q.1.6) to home-monitor gout flares real-time.

Methods
This prospective feasibility study (NL6435) recruited thirty patients during their outpatient visit at the rheumatology ward. Inclusion criteria were age ≥ 18 years, in possession of a smartphone, diagnosis of crystal proven gout or a high clinical suspicion of gout and at least one (possible) flare reported in the last three months.

Q1.6 is a straight-forward query app that has been customised to incorporate a modified version of the 2017 four-criteria gout flare definition. For 90 consecutive days the Q1.6 app asked current pain score on a 0 to 10 scale as screener question. Scoring pain below four terminated the query, otherwise the app posed the remaining three gout flare definition criteria: does the patient experience warm and/or swollen joints and does he/she regard this as a flare. Responses were transmitted to the clinicians dashboard real-time. Alerts to the rheumatologist/pharmacist were generated when a participant reported a flare, scored pain above three for three consecutive days or was inactive for five days.
End of study evaluation consisted of a questionnaire assessing ease of use and perceived usefulness, based on the Technology Acceptance Model. Additionally patient value was assessed by tracking app use, generated alerts and actions taken. All constructs were analysed using descriptive statistics.

(Preliminary) Results

The trial started in November 2018, on August 1st 2019 inclusion was complete and 22 had finished follow-up. None have prematurely quit. There have been three minor technical issues which were resolved by the researcher. Of 1980 questions that have been posed 78 responses were missed (3,9%). Thirty alerts were recorded in eight patients. Nineteen pro-active telephone calls were made which resulted in two visits to the clinic within 48 hours, one intra-articular injection, one diagnostic screening, eight medications started, and three medication adjustments.

Conclusion

This prospective study assesses feasibility of using an app for home-monitoring of gout flares in 30 patients. Preliminary results in 22 patients are encouraging regarding technical functionality, query adherence and app attrition. If our electronic application proves feasible and accurate it can improve ascertainment of gout flares in daily practice which is a significant gap in the field.

ITERATIVE DESIGN PROCESS OF A SERIOUS GAME APPLICATION FOR IMPROVING MEDICATION ADHERENCE

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Background

The benefits of medication can only be achieved when patients adhere to the agreed regimen. From previous studies it is known that patients encounter practical and psychological barriers (both explicit and implicit) to achieve optimal medication adherence. Applying games to implicitly target medication-taking behaviour by combining the entertainment of puzzling with medication related triggers might be successful in improving medication adherence. This study aimed to develop such a serious game application called 'Medi & Seintje' through an iterative design process.

Methods

'Medi & Seintje' was developed in two rounds of four weeks with each round consisting of a development, (user-)testing, adaptation, and re-testing phase. The Technology Acceptance Model (an information systems theory that models how users come to accept and use new technology) was used to assess usefulness (GameFlow), ease of use (System Usability Scale; SUS), attitude toward using and actual use (Google Analytics). All constructs were analysed using descriptive statistics. The study aimed to include fifty patients from the Sint Maartenskliniek in Nijmegen. Inclusion criteria were age ≥ 16 years, use of disease-modifying antirheumatic drugs, proficiency in the Dutch language and possession of smartphone or tablet.

Results

Fifty-four patients were included and divided over two groups to assess different constructs during each round. GameFlow ratings indicated that patients regarded the application as fairly useful. SUS scores in both rounds were 65 (out of 100). Attitude toward using was assessed by scoring the application and its login system and by asking suggestions for improvement. Attitude toward using the app in general scored 54 and 57 points (out of 100), whereas the login system scored 27 and 31 points in round one and two respectively. All mean scores showed a large standard deviation indicating a broad spectrum of views. Output of Google Analytics learned that 19 and 22 patients used the application in round one and two respectively, of which 12 in both rounds. Mean (± SD) daily session duration was 11.4 ± 8 minutes during round one and 16 ± 2.9 minutes during round two.

Conclusion

The iterative design process of serious game application 'Medi & Seintje' led to valuable insights in patient acceptance, usability and suggestions for improvement. Consequently, the latest version of the application complies with the needs of end-users. A randomised clinical trial (the

GAMER study – NL7217) has recently started to assess the effect of playing 'Medi & Seintje' on medication adherence.

PATIENTS' VIEWS ON SELF-ADMINISTRATION OF MEDICATION DURING HOSPITALISATION: A MIXED-METHOD STUDY

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Background
Self-administration of medication by patients during hospitalisation could positively affect medication safety, medication adherence, patients' understanding about their medication, and medication waste. Successful implementation of self-administration of medication strongly depends on patients' willingness thereof. This study aimed to identify the views of patients towards self-administration of medication during hospitalisation and to assess patients' willingness thereof.

Methods
A mixed-method study was conducted among adult hospitalised patients in four Dutch hospitals. Firstly, qualitative semi-structured interviews were conducted with patients to identify their views towards self-administration of medication, including (dis)advantages thereof, and preconditions that should be met. Interview transcripts were subjected to thematic-content analysis. Thereafter, these outcomes were used to construct a quantitative questionnaire that was distributed among hospitalised patients. Patients were asked to report their willingness towards self-administration of medication and socio-demographic characteristics. The main outcome was the proportion of patients that was willing to perform self-administration of medication. Data was descriptively analysed.

Results
Nineteen hospitalised patients (mean [standard deviation; SD] age = 61 [13.4] years old; 52.6% male) were interviewed. Most patients had a positive view towards self-administration of medication during hospitalisation. Reported advantages included recognition of medication, increased knowledge on medication, awareness about medication management, autonomy, trust in pharmacotherapy, time saved by nurses, and medication waste reduction. Few disadvantages were identified, which included safety concerns when patients are not capable of self-administration and lower medication recognition by nurses. Preconditions that should be met were assessing patient's eligibility for self-administration (based on health condition), having a choice to participate in self-administration of medication, and monitoring of medication intake by nurses.
A total of 210 patients (mean [SD] age = 66.7 [13.2] years old; 54.8% male) participated in the survey. Of these, 116 (55.2%) were willing to self-administer medication. Patients' preferences were medication administration by nurse (49.5%), themselves (39.5%) and no preference (11%) respectively.

Conclusion
Patients tend to have positive views towards self-administration of medication when several preconditions are met. When theoretically proposed to self-administer medication during hospitalisation, around half of patients is willing.

SELF-ADMINISTRATION OF MEDICATION DURING HOSPITALIZATION: A QUALITATIVE STUDY AMONG STAKEHOLDERS

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Background
Implementation of self-administration of medication during hospitalization is likely to increase patient safety and patient involvement. To implement self-administration of medication, knowledge of stakeholders' views on self-administration of medication and prerequisites for implementation are warranted. This study aimed to identify stakeholders' views on self-administration of medication during hospitalization and prerequisites for implementation.

Methods
A qualitative study was conducted among Dutch stakeholders using semi-structured interviews between April and July 2019. Participants were representatives of health care professional organizations (pharmacists, prescribers, nurses), health care provider organizations (of different hospital types), health authorities, health insurers, and a patient representative organization. Stakeholders were asked about their views on the current medication handling

in Dutch hospitals, on self-administration of medication, and on the implementation of self-administration of medication. Data were analyzed using thematic analysis.

Results

Fourteen interviews with stakeholders were held, from which three main themes were identified: general views about self-administration of medication, prerequisites that should be met, and practical requirements to implement self-administration of medication. General views about self-administration of medication varied from either being positive to hesitant and negative but were mostly positive. Most stakeholders stated that implementation of self-administration of medication is feasible, however, concerns were frequently related to the feasibility of implementing the process in practice. Prerequisites that should be met before implementation included scientifically demonstrating the added value compared to usual care, guaranteeing patient safety, guaranteeing legal feasibility without double funding, and defining stakeholders' responsibilities in the process. Practical requirements to implement self-administration of medication included communication towards patients, e.g. instructions about new medication during admission, and adjusting the organizational hospital infrastructure, e.g. providing patients with their own medication if they run out of stock.

Conclusion

Although stakeholders views about self-administration of medication were ambivalent, most stakeholders were positive about the concept of self-administration of medication. Implementing self-administration of medication is achievable provided that the prerequisites identified in this study are met. To make self-administration of medication successful the practical requirements should be acknowledged.

ROBOTIC COMPOUNDING VERSUS MANUAL COMPOUNDING OF CHEMOTHERAPY: COMPARING DOSING ACCURACY, MICROBIOLOGY, AND ENVIRONMENTAL CONTAMINATION

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Background

Compounding of cytostatic drugs requires strict aseptic procedures, while exposure of hospital staff to hazardous drugs should be minimized. To automatically produce ready-to-administer products we purchased the robotic system APOTECAchemo (Loccioni Humancare, Italy).
The aim of our study was to investigate the microbiological safety of the robot, and to compare the dosing accuracy and environmental contamination of the robot with those of manual compounding.

Methods

To measure the accuracy, 40 methotrexate (MTX) 50mg in 50ml infusion bags and 40 cyclophosphamide 1200mg in 100ml infusion bags were prepared with the robot and by manual procedure. Dosing accuracy was measured by weighing and by measuring the drug concentrations with an HPLC-method.
Aseptic compounding was simulated in the robot with media fills (n = 96) and the reuse of vials was tested by compounding 300 syringes by repeated withdrawal of 15ml media on six consecutive days from the same 50 vials. In the manual procedure we used spikes, which cannot be removed from vials after use, making a comparison between the two compounding methods impossible.
To measure environmental contamination, wipe samples from the cleanroom and the surface of infusion bags were collected, and analyzed for the presence of 5-FU and cyclophosphamide.

Results

The accuracy of 50mg MTX and1200mg cyclophosphamide compounding was comparable for the robot and the manual procedure (49.1 mg, SD = 0.9 mg and 50.5 mg, SD = 3.8mg respectively for MTX; and 1126 mg, SD = 44 mg and 1138 mg, SD = 46.7mg respectively for cyclophosphamide).
None of the prepared media fills by the robot showed any contamination. Moreover, it showed that it is safe to reuse the same vial for up to six times on up to seven days.
In the contamination study, a total of 284 wipe samples were collected (113 from the manual and 171 from the robotic process). External cross-contamination occurred in 2.5% of manually prepared bags and 1.25% of robotic bags. The robot results showed remaining cytotoxics after cleaning, necessitating extension of the cleaning procedure and the introduction of a workplace cover under the dosing device. Thereafter, additional samples were taken, showing 0% cross-contamination and 0% environmental contamination after cleaning.

Conclusion

Compounding of cytotoxics with the robot as well as by hand produces accurate chemotherapy doses, without microbiological contamination. Robotic compounding

shows advantage over manual compounding in the ability to safely reuse vials, and to compound non-cytotoxic drugs such as monoclonal antibodies in the same setting as chemotherapy.

MEDICATION-RELATED PROBLEMS IN LIVER TRANSPLANT PATIENTS IN THE NETHERLANDS

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Background

Liver transplantation has been a rapidly growing field over the past 40 years. After transplantation, liver transplant (LTx) recipients receive medical care to promote survival of the transplanted liver. Currently, about 2000 LTx recipients are being followed after transplantation in the Netherlands. Due to the development of comorbidities, LTx recipients will receive more medicines over the years. Moreover, adherence to immunosuppressive medication and avoidance of contra-indicated drugs is essential for long-term survival. Therefore, signalling and treatment of medication-related problems (MRPs) in LTx recipients opens opportunities to improve medication safety. This study aimed to investigate the prevalence and types of MRPs and interventions initiated by a hospital pharmacist (HP) in a cohort of stable LTx recipients in the outpatient setting.

Methods

This study was a prospective, observational study conducted between September – December 2018 at the ErasmusMC in LTx recipients that visited the outpatient clinic for an annual extensive check-up. A 20-minutes face-to-face consultation with a HP was part of this check-up and consisted of medication reconciliation and a structured conversation about medication, adherence, adverse drug reactions (ADRs) and drug use. Potential interventions were discussed with the patient and hepatologist and initiated by the HP. The MRPs and interventions were registered by the HP and categorized into predefined categories. Analysis was performed using descriptive statistics.

Results

The HP consulted 64 LTx recipients with a median age of 59.5 years (IQR = 47-66) and a median of seven medications. Frequent comorbidities were chronic kidney disease (n = 26), cardiovascular disease (n = 26), and diabetes mellitus (n = 19). In 57.8% of the patients, one or more discrepancies were found in the medication registered in the hospital and actually used by the patient. Most discrepancies (60.4%) were missing medications.
In total, 98 MRPs were identified in 53 patients, with a median of 2 MRPs per patient. Most frequent MRPs were: ADRs (22.4%), nonadherence (19.3%), unnecessary drugs (16.3%) and untreated indications (12.2%). Interventions most frequently proposed were: optimizations in dosage regimen (21.2%), medication compliance advises (16.8%) and stopping of medication (12.4%). Most interventions proposed by the HP (93.6%) were followed by both patients and hepatologists.

Conclusion

In this cohort, LTx recipients experience a median of two MRPs of which ADRs, nonadherence and unnecessary drugs are most frequently reported. An outpatient monitoring program of a HP for LTx recipients can signal MRPs and lead to interventions that are accepted by both patients as hepatologists and hence contribute to medication safety in LTx recipients.

SEX AS A RISK FACTOR FOR CLINICALLY RELEVANT ADVERSE DRUG REACTIONS

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Background

Adverse drug reactions (ADRs) are a major health concern and responsible for approximately 5% of all acute hospital admissions. Studies suggests that women are 1.5-1.7 times more likely to develop ADRs than men [2]. The main objective of this study was to investigate whether sex is an independent risk factor for ADRs resulting in hospitalizations, and which sex is more prone to develop a particular ADR.

Methods

Patients are selected from the PHARMO Database Network. Selected hospital admissions from 2005 to 2017 are coded as ICD 9 (E930-E949, from 2005 to 2012) or ICD 10 (Y40-Y59, from 2013 to 2017) as a secondary diagnosis. These codes indicate an ADR of a drug group used in a therapeutic dose. Only patients with a corresponding drug, based on the Anatomical Therapeutic Chemical classification, delivered within three months before the

hospitalization are included. Within these drug groups we studied the most frequent ADRs for both men and women, excluding sex-specific ADRs such as uterine or prostate problems. Odds ratios (ORs) with 95% CI for combinations of a drug group (secondary diagnosis) and an ADR (primary diagnosis) with at least 50 hospital admissions for women or men were calculated with respect to the total number of users and adjusted for age.

Results

In total there are 18,469 hospital admissions, 0.35% of the total number of hospitalizations, involving women and 14,678 admissions, 0.35% or the total number of hospitalizations, involving men due to an ADR. For 48 drug-ADR combinations ORs are calculated. There are 18 combinations with a significant OR of which ten combinations with a greater risk in women and eight in men. The most distinct differences are seen in ADRs due to anticoagulants and diuretics. Anticoagulants show a higher risk of a hospital admission with haematuria, haemoptysis, subdural haemorrhage in men and a higher risk of rectal bleeding in women. Also, there is a higher risk of hospital admission involving women using diuretics that caused hypokalaemia and hyponatraemia.

Conclusion

Sex might be a risk factor for ADR-related hospitalizations and should be taken into account in further research.

REAL-WORLD OUTCOMES OF METASTATIC RENAL CELL CARCINOMA TREATMENTS FROM ELECTRONIC HEALTH RECORDS: RESULTS OF A TEXT MINING APPROACH VERSUS MANUAL REVIEW

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Background

Real-world data (RWD) are necessary to complement data from randomized clinical trials on outcomes of new oncologic therapies. Manual review, the standard collection method of collecting RWD from electronic health records (EHR), is time-consuming and error-prone. CTcue Clinical Data Collector (CDC) is a software package that assists EHR review by text mining and automatic data collection. The aim of this study is to validate CDC as RWD collection method for oncologic treatments.

Methods

A retrospective cohort study of patients with metastatic renal cell carcinoma treated with cabozantinib, pazopanib, sunitinib, everolimus or nivolumab was performed using CDC and manual review. Patients were included between January 2015 until May 2019 in the Leiden University Medical Center. Patient characteristics and treatment outcomes were collected per treatment from EHR. As validation, data collected using CDC was compared to manual review. Survival outcomes were compared with Kaplan Meier, for categorical patient characteristics and side effects Cohen's kappa was calculated. For continuous patient characteristics Bland-Altman plots were composed. Also, mean data collection time per patient was calculated.

Results

CDC as well as manual review identified 100 patients with a match of 99 patients, an overlap of 174 out of 176 treatments was found. Agreement between patient characteristics sex, nephrectomy status and comorbidities diabetes mellitus II and COPD was strong (kappa of 1, 0.93, 0.88, and 0.8), age, kidney- and liver function, weight and length showed mean differences of 0.03% to 1.3%. However, agreement was weak for pre-existing hypertension and side effects hand-foot syndrome, liver toxicity and hypertension (0.32, 0.47, 0.48, and 0.43). Calculated median overall survival were 28.2 months (95% CI = 22.2-34.3) versus 28.3 months (95% CI = 22.8-33.7) and progression-free survival 9.3 months (95% CI = 5.86-12.7) versus 7.1 months (95% CI = 5.2-9) for CDC versus manually review.
Mean data collection time per patient using CDC was 12 minutes versus 86 minutes for manual review.

Conclusion

Collection of RWD on oncologic treatments using CDC versus manual review showed non-significant differences for matching of patients, most patients characteristics and survival outcomes with a sevenfold reduction of time invested per patient. Although further improvement is needed on variables with a weak level of agreement we believe CDC is a promising tool to collect RWD.

THE IMPACT OF CLINICAL PHARMACIST DRIVEN INTERVENTIONS ON PATIENT SAFETY IN HOSPITALIZED PATIENTS; PRELIMINARY RESULTS OF A POINT PREVALENCE STUDY

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Background

Most patients admitted to a hospital use more than five drugs. Besides the beneficial effects of these drugs, these patients are at risk for medication errors. Traditionally hospital pharmacists use clinical decision support systems (CDSSs) and clinical rules in order to prevent drug-related problems (DRPs). For specific specialisms, for instance intensive care and paediatric care, it has been shown that the involvement of clinical pharmacists integrated in the medical team on the ward has a beneficial effect on the reduction of DRPs. Hence, there is a shift from the traditional way of practice to integration of clinical pharmacists in the medical team on the ward. However, the impact of hospital-wide integration of clinical pharmacists on patient safety is not clear.

Methods

In this observational point prevalence study, interventions made by clinical pharmacists (on top of the interventions based on clinical rules or CDSSs) were studied during five consecutive working days. Patients admitted to the ErasmusMC University Medical Center for more than 24 hours were included. The following endpoints were recorded: type of intervention, reason for intervention, severity of the underlying drug-related problem (using the NCC MERP index scale [3]), proportion of interventions accepted by the physician, communication route and time investment.

Results

A total of 238 medication reviews were conducted and the pharmacists were consulted 16 times. For 58.4% of the reviewed patients potential DRPs were detected, with an average of 1.8 per patient. Overtreatment was the most reported DRP (31.6%), subsequently the most common type of intervention was the advice to stop medication (43.2%). During the study 16 % of the interventions were categorized as no error, 62% as error, no harm and 22% as error, harm. 66.6% of the interventions were accepted and given a follow-up. Face to face was the most frequently used method of communication, 56.9%. The average time investment was 8.6 minutes per medication review.

Conclusion

Structured medication reviews by clinical pharmacists contribute to detection and resolution of DRPs, mainly by reducing overtreatment. Therefore, in addition to clinical rules or CDSSs, a hospital-wide integration of clinical pharmacists as part of the multidisciplinary team can improve medication safety and optimize pharmaceutical care.

PREVALENCE OF MEDICATION TRANSFER ERRORS IN NEPHROLOGY PATIENTS AND POTENTIAL RISK FACTORS

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Background

Medication reconciliation in transitions of care can prevent medication transfer errors (MTE). MTE can cause patient harm. Since performing medication reconciliation for every patient is not always feasible, identification of potential risk factors of MTE could aid in targeting this intervention to the right patients.

Objective

To establish the proportion of patients with one or more MTE in the outpatient nephrology setting. Secondary patient characteristics associated with MTE, type and potential harm, and medication groups were investigated.

Methods

This retrospective observational cohort study was conducted in the Leiden University Medical Center, the Netherlands, between November 2017 and April 2018. The cohort involved patients in whom medication reconciliation was performed by a medical attendant using the electronic tool 'Medical Dashboard' prior to visiting the nephrologist. MTE were defined as unintended discrepancies between the medication in the hospital system and the result of the medication reconciliation. The proportion of patients with one or more MTE was calculated and the association of patient characteristics (age, sex, number of medications and kidney function (CKD-EPI)) with MTE was analyzed using multivariate logistic regression.

Results

Of 380 patients, 235 patients (61.8%) had at least one MTE. On average patients used 10.3 medications. The number of medications per patient was significantly associated with MTE; OR = 1.11 (95%CI = 1.05-1.16). No association was found for age, sex, and kidney function.

Conclusion
In ambulatory nephrology patients 61.8% had at least one MTE. Nephrology patients using a higher number of drugs are more prone to MTE.

E-CONSULTS TO IMPROVE ACCESS TO THE HOSPITAL PHARMACIST: ANALYSIS OF TWO YEARS' EXPERIENCE

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Background
Clinical patients as well as patients visiting the outpatient clinic of the Leiden University Medical Center have insight into their electronic health record including their medication in the Electronic Patient Portal. In addition, patients are offered to easily ask questions about their medication directly to a hospital pharmacist by using the E-consult function within the Patient Portal. To further improve the use of E-consults, information regarding the patient population and their needs is studied.

Methods
E-consults sent to the hospital pharmacist between March 2017 until August 2019 were analyzed. Patient characteristics such as age, sex and the number of medications used were collected. Furthermore we looked into the appropriateness of the E-consults for the hospital pharmacist, the time of sending as well as the subject of the E-consults.

Results
During the study period 247 E-consults were received, from which 167 E-consults (involving 167 patients) could be analyzed. Of these, 47/167 (28.1%) did not involve medication or were not intended for the hospital pharmacist. The average age of the patients was 53 (SD = 16,7) and 78 patients (46,7%) were male. Ninety patients (53.9%) used < 5 medications; 52 (31.1%) used 5 to 9 medications and 25 (15%) used ≥ 10 medications. Patients from 26 different medical specialties sent E-consults to the hospital pharmacist from which the most common specialty was Cardiology with 36 patients (21.6%). 109 (64.7%) of E-consults were sent during office hours. E-Consults concerned: questions and updates on the medication overview (33/120); availability of medication (32/120); efficacy and adverse effects (22/120); use of medication (17/120); traveling (6/120); other subjects (10/120).

Conclusion
Introducing E-Consults facilitates patients to directly ask medication-related questions to hospital pharmacists. Patients varied in age and sex as well as the number of drugs they were using. To facilitate the E-consult tool in the future different categories may be added to the Electronic Patient Portal clarifying what questions patients can ask to hospital pharmacists and which questions are more intended for medical specialists.

AN INTERNATIONAL QUALITY CONTROL PILOT PROGRAM FOR THE MEASUREMENT OF ANTIMICROBIAL DRUGS

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Background
There is an increased interest in developing assays to determine plasma/serum concentrations of antimicrobial drugs. Assays for antimicrobial drugs are used for pharmacokinetic research purposes as well as in clinical practice when performing TDM. Participation in an interlaboratory quality control (QC) program is an essential component of quality assurance. Whereas QC programs for aminoglycosides and glycopeptides have been in place for several years, there is no independent, international program for external QC of other antimicrobial drugs. Therefore, we developed an international QC program for the measurement of antimicrobial drugs.

Methods
Antimicrobial drugs involved in the first two rounds of this pilot program were ceftazidime, ciprofloxacin, flucloxacillin, piperacillin, tazobactam, sulfamethoxazole, n-acetyl sulfamethoxazole and trimethoprim. Two QC samples (one sample per round) were prepared by spiking drug-free plasma with all eight antimicrobial drugs in either low or high concentrations, all within the clinical exposure range. Samples were dispatched at dry ice in view of the instability of some of the drugs. All participants were provided feedback anonymously on their performance.
All weighed-in concentrations were considered true values. Acceptable accuracy was defined if measurements were within the 80-120% limits of the true weighed-in concentrations. A one-tailed unpaired t test was performed on the absolute inaccuracies to determine a difference between the high versus low concentrations.

Results

143 laboratories were approached. 17 laboratories participated in the first round and 22 laboratories participated in the second round. A total of 129 analyses were performed in both rounds. A total of 81% (range = 56-100%) of the measurements were determined accurately.

The measurements of flucloxacillin showed the best performance; 100% (21 out of 21) of the samples were determined accurately. The measurements of ceftazidime showed the worst performance; 56% (14 out of 25) of the samples were determined accurately. The measurements of the higher antibiotic concentrations showed a trend towards better performance than of the lower concentrations (P = 0.052).

Conclusions

The initial results of this pilot program showed a relatively good performance of the participating laboratories compared to previous program initiated by us (HIV, TB and fungal). Nevertheless, still one out of five (19%) measurements was inaccurate. By participating in the program these laboratories were alerted, which may help them to improve their methods. Our results emphasize the importance of an ongoing QC program. In future rounds we will consider incorporating other antimicrobial drugs as well as the possibility the report free concentrations.

IMPROVED EARLY TREATMENT RESPONSE OF ECULIZUMAB WITH A PATIENT-FRIENDLY DOSING SCHEME IN ADULT PATIENTS WITH ATYPICAL HEMOLYTIC UREMIC SYNDROME

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Background

Eculizumab is a very expensive humanized monoclonal antibody against complement protein C5 for the treatment of atypical hemolytic uremic syndrome (aHUS). The approved dosing regimen of eculizumab consists of an initial phase (900 mg eculizumab weekly for 4 weeks) followed by a maintenance phase (1200 mg in the fifth week and every 14 days thereafter). Therapy is monitored by eculizumab trough concentrations (target = 50-100 mg/L) and classical pathway (CP) activity levels (target < 10%). Recent data show that exposure is often sub-therapeutic after the first dose, while being supra-therapeutic when starting the maintenance phase. Early adequate therapy is highly recommended to stop thrombotic microangiopathy and to prevent chronic sequelae. Therefore, we aimed to develop a dosing strategy to improve early treatment response and patient-friendliness at, preferably, lower costs.

Methods

Pharmacokinetic (PK) and pharmacodynamic (PD) data from 30 aHUS patients were available, consisting of 647 eculizumab time-concentration data and 504 CP activity levels. PK-PD modeling was performed by means of non-linear mixed effects modeling. The final model was used to investigate alternative initial phase dosing strategies through Monte Carlo simulations in 1000 virtual patients. The optimal strategy was defined as the strategy with the highest percentage of patients with a CP < 10%, without increasing the cumulative dose during the initial phase.

Results

A PK-model with parallel first order and Michaelis-Menten elimination rates best described the data. The estimates of the model were clearance 0.167 L/day (RSE = 6%), volume of distribution 7.11 L (RSE = 8%), maximum rate (V_{max}) 27.7 mg/day (RSE = 6%), plasma concentration for 50% of maximum rate (K_m) 20.8 mg/L (RSE = 28%). The PK-PD relation was described with an inhibitory E_{max}-model, with an estimated maximum inhibition (I_{max}) of 0.941 (RSE = 1%), a concentration for 50% inhibition (IC_{50}) 21.3 mg/L (RSE = 17.1%) and Hill Coefficient of 4.5 (RSE = 12%). A weight-based weekly loading dose (< 60kg = 1500 mg, 60- < 90 kg = 1800 mg, 90- < 120 kg = 2100 mg, and ≥ 120 kg = 2400 mg) on day 1, followed by 1200 mg on day 14 and 28 was found to improve treatment response. In total, 96.6% of the virtual patients reached the CP target on day 7, compared to 81.3% with standard dosing. This also resulted in a dose reduction of 12.5% compared to the first 28 days of the approved weekly induction dosing regimen.

Conclusion

A patient-friendly weight-based dosing strategy results in better treatment response during the initial phase at lower costs (~10.000 euro savings per patient).

THE EFFECT OF THE ANTICHOLINERGIC BURDEN ON DURATION AND SEVERITY OF DELIRIUM IN OLDER HIP SURGERY PATIENTS WITH AND WITHOUT HALOPERIDOL PROPHYLAXIS: A POST-HOC ANALYSIS

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Background
Anticholinergic acting drugs have been associated with delirium in older patients. The aim of this study was to explore the association between the anticholinergic burden and the duration and severity of delirium in older hip surgery patients with or without haloperidol prophylaxis.

Methods
Older patients with a postoperative delirium following hip surgery from a randomized controlled trial investigating the effects of haloperidol prophylaxis on delirium incidence were included in this study. The anticholinergic burden was quantified using two different tools, the Anticholinergic Drug Scale and an Expert Panel. Using linear regression, the association between the anticholinergic burden and delirium was analyzed.

Results
Overall delirium duration and severity were not significantly associated with the ACB. Also, no statistical significant differences were found in delirium duration or severity between the placebo and haloperidol treatment groups for the anticholinergic burden groups. The protective effect of haloperidol on delirium duration and severity however tended to be present in the patients with no or a low ACB but not or to a lesser extent in patients with an intermediate to high ACB.

Conclusion
The ACB was not significantly associated with delirium duration or severity. Haloperidol prophylaxis tended to shorten delirium duration and decrease delirium severity in patients with no or a low ACB. To further explore the influence of anticholinergic acting drugs on delirium duration and severity and the effect of concomitant haloperidol use, additional research with a higher haloperidol dose, a larger study population and ACB quantification taking drug exposure into account is warranted.

THE SAFETY AND EFFECTIVENESS OF AN ANTIBIOTIC STEWARDSHIP INTERVENTION IN HOSPITALIZED PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA: A STEPPED-WEDGE CLUSTER RANDOMIZED TRIAL

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Background
Dutch guidelines recommend penicillin or amoxicillin for moderately-severe community-acquired pneumonia (CAP). In clinical practice guideline adherence is low and many patients receive broad-spectrum antibiotics. We aimed to determine safety and effectiveness of a multifaceted antibiotic stewardship intervention to reduce broad-spectrum antibiotics in patients hospitalized with CAP.

Methods
We performed a stepped-wedge cluster randomized trial in 9 Dutch hospitals (NCT02604628). The intervention consisted of education (e.g. e-learning, clinical lessons), audit and feedback and motivation of opinion leaders. The co-primary outcomes were days of therapy (DOT) with broad-spectrum antibiotics (effectiveness) and all-cause 90-day mortality (safety). Narrow-spectrum antibiotics was defined as penicillin, amoxicillin or doxycyclin monotherapy All other were defined as broad-spectrum. The study database was locked on 12 February 2019. We performed an intention-to-treat analysis using a non-inferiority margin of 3% and a one-sided alpha of 0.05 for 90-day all-cause mortality and a superiority analysis for differences in medians of broad-spectrum DOT.

Results
From November 2015 till November 2017 4084 patients were included; 2240 in the pre-intervention and 1,844 in the intervention period. Median (range) age was 73 (18-101) years, 53% (2163/4084) were male and mean (± SD) PSI score was 91.3 (± 31.4). Median (IQR) DOT with any antibiotic was 8 (7-10) and 8 (7-11) in the pre-intervention and intervention period, respectively. Median (IQR) narrow-spectrum DOT was 0 (0-6) in the pre-intervention and 5 (0-8) in the intervention period. Median (IQR) broad-spectrum DOT was 6 (2-9) in the pre-intervention and 3 (0-8) in the intervention period. The adjusted relative reduction in broad-spectrum DOT during intervention was 26.9% (95% CI = 14.5%-37.5%) from an average of 6.6 days in the pre-intervention period to an average of 4.8 days in the intervention period. Crude 90-day mortality was 10.8% (242/2233) and 10.8% (199/1836) during pre-intervention and intervention period. In intention-to-treat analysis adjusted absolute difference in 90-day mortality was 0.3% (90% CI = –2.9-2.2) for the pre-intervention versus intervention period, indicating non-inferiority for all-cause mortality.

Conclusion
In patients hospitalized with moderately-severe CAP a multifaceted antibiotic stewardship intervention safely reduced the days of broad-spectrum antibiotic use with 27%.

PHARMACOKINETIC-PHARMACODYNAMIC TARGET ATTAINMENT OF CIPROFLOXACIN IN ADULT PATIENTS ON GENERAL WARDS WITH ADEQUATE AND IMPAIRED RENAL FUNCTION

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Background

There are no prospective data on pharmacokinetic-pharmacodynamic (PK-PD) target attainment after the guideline-recommended dose reduction of the antibiotic ciprofloxacin in patients with impaired renal function (eGFR < 30 mL/min). This study aims to investigate PK-PD target attainment of the ratio of the area under the concentration-time curve over the minimum inhibitory concentration (AUC/MIC) ≥ 125 in patients with adequate and impaired renal function receiving regular and reduced doses of ciprofloxacin.

Methods

In this prospective observational cohort study adult patients on general wards of a Dutch university hospital were included when treated with ciprofloxacin. Three blood samples per patient were prospectively obtained for ciprofloxacin concentration measurement in the first 48 hours of treatment, complemented with samples from waste material. AUC calculation was performed using a population PK model developed by non-linear mixed effects modelling.

Results

A total of 40 patients were included, of which 8 patients with impaired renal function who were all treated with a guideline-recommended reduced dose of ciprofloxacin. Using the clinical breakpoint MIC of most isolated bacteria (0.25 mg/L), the $AUC_{0\text{-}24}$/MIC ≥ 125 was attained in 38% of patients with adequate renal function receiving a regular dose and in 13% of patients with impaired renal function receiving a reduced dose. Median drug exposure in the first 24-hours of treatment ($AUC_{0\text{-}24}$) for patients with impaired renal function receiving a reduced dose was 17.9 mg/L*h, which was statistically significantly lower than the median $AUC_{0\text{-}24}$ for patients with adequate renal function receiving a regular dose (29.4 mg/L*h, P < 0.01).

Conclusion

$AUC_{0\text{-}24}$/MIC ≥ 125 is not attained in the majority of adult patients on general wards for clinically relevant bacteria with MIC values at or just below the clinical breakpoint. Also, ciprofloxacin exposure in patients with impaired renal function receiving the guideline-recommended reduced dose is significantly lower than in patients with adequate renal function receiving the standard ciprofloxacin dose.

3D PRINTING OF TABLETS FOR INDIVIDUAL PAEDIATRIC PATIENTS

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Background

Commercially available tablets often don't meet patient's needs, as can be the case for children. 3D printing can possibly achieve this. The most commonly used technique requires a high processing temperature (> 100 oC) and most polymers lack an immediate release profile. This proof-of-principle study investigates a novel, lower temperature 3D printing technique. It aims to produce tablets of different dosages for children, with adequate content uniformity and an immediate release profile. Furosemide was used as this is frequently used in the hospital but, only a solution is available for children.

Methods

Placebo tablets were printed to establish critical process parameters of the technique and assess reproducibility. A semi-crystalline polymer was used as carrier. Weight distribution (Ph.Eur.2.9.5) and tablet dimensions were critical quality attributes. Formulations were printed and analysed for content uniformity (Ph.Eur.2.9.40) and dissolution profile (Ph.Eur.2.9.3) using high-performance liquid chromatography (HPLC-UV) and UV/Vis spectrophotometry, respectively. The tablets were further analysed for thermal and physical properties using thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) and scanning electron microscopy (SEM).

Results

Printing temperature and layer heights were found to be the most important critical process parameters. Tablets were reproducible with an average diameter (SD) of 7.24 (0.0865) mm, average height (SD) of 3.18 (0.0571) mm. The weight distribution complied with a relative standard deviation of 1.74-2.23%. Formulations containing 2 or 10 mg furosemide and 5% w/w polysorbate 80 were printed successfully. The formulation ratios were

determined empirically. Both dosages had adequate content uniformity (acceptance values 12.9 and 6.6). Both formulations showed an immediate release profile indicating case II drug transport. TGA, DSC and SEM suggested the tablets were solid dispersions. TGA indicated no thermal degradation of the formulations and raw materials at printing temperature. DSC showed furosemide acted as a plasticiser.

Conclusion

This proof-of-principle study shows this lower temperature 3D printing technique can be useful in enabling personalised medicine. Tablets of different dosages could be printed with a relatively easy and flexible method. Content uniformity and dissolution testing for immediate release complied to compendial standards. The tablet dimensions, and the possibility for flexible and accurate dosing, makes these tablets suitable for children. Furosemide, a BCS class IV drug, can furthermore possibly benefit from this dosage form as a solid dispersion.

EVALUATION FOR SPLITTING A SINGLE-TABLET REGIMEN TO A TWO-TABLET REGIMEN CONTAINING THE SAME ANTIRETROVIRALS: ACCEPTANCE, ADHERENCE, QUALITY OF LIFE AND COST-SAVINGS

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Background

Combination antiretroviral therapy (cART) is used by an increasing number of HIV-infected individuals, for increasing lengths of time. cART is responsible for a large proportion of chronic HIV-care costs, use of generic ART could lead to significant cost reduction. Changing therapy from a single-tablet regimen (STR) to a two-tablet regimen (TTR) could save up to 30% of ART costs, equivalent to €3,000 per patient per year. The objectives of the SPLIT-project are to study patient acceptance of splitting HIV-medication; patient adherence when splitting an STR to a TTR, quality of life in HIV-infected patient, and cost-savings.

Methods

All HIV-infected patients on branded Triumeq, Atripla (also generic) or Eviplera in the HIV treatment centers of Radboudumc, Amsterdam UMC location AMC, Rijnstate, Isala and OLVG hospital were eligible for this study (December 2018- September 2019). Patients were informed by healthcare providers to split their STR to a TTR ("opt-out"). After inclusion, patients had a free choice to split and reason for splitting was documented. An electronic validated questionnaire was sent to study patient acceptance, self-reported drug adherence and quality of life (SF12). After three and twelve months questionnaires were repeated. Cost savings were calculated using Dutch drug prices. This first analysis reports on the acceptance rates of splitting, baseline data for patients' views on their current medication, and initial costs savings.

Results

A total of 262 patients were included in the study. One hundred forty-three of 262 patients (55%) agreed to split to TTR. In the first 6 months of follow-up, 12 out of 143 (8%) patients switched back to branded medication due to perceived mild side-effects. Baseline results of questionnaires (n=143) showed a high quality of life and acceptance for the satisfaction about the HIV treatment: all patients scored maximal or sub-maximal satisfaction for 7 out of 10 questions. Furthermore, no issues were reported with adherence. During the first 6 months of follow-up drug expenses were €153.401 lower compared to the STR drug expenses.

Conclusion

A pro-active policy for splitting a STR to a TTR in HIV-infected patients was successful. First data show a reasonable patient acceptance of treatment at baseline. Only 8% of patients switched back to a single-tablet regimen within 3 months after splitting. Patients infected with HIV appear to be open for changing their STR medication to TTR.

EARLY-LIFE ANTIBIOTICS USE AND SUBSEQUENT RISK OF CHILDHOOD ASTHMA AND ECZEMA: A DISCORDANT TWIN STUDY

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Background

Epidemiological studies have investigated whether early-life exposure of antibiotics increases the risk of asthma and eczema, but unmeasured confounding was difficult to

assess. We aimed to study the relation between early-life antibiotic use and asthma/eczema development using a twin design to assess confounding.

Methods

We investigated children (3-10 years) from the Netherlands Twin Register (NTR, n = 34,352) and replicated the study at age 9 in the Swedish Twin Register (STR, n = 7,906). Use of antibiotics was recorded at age 0-2 years. Asthma and eczema outcomes were parent reported. Individuals derived from twin pairs were included in unmatched analyses followed by a co-twin control analysis with disease discordant twin pairs. A comparison within twin pairs allows us to control for shared environment, and a comparison of monozygote (MZ) with dizygote (DZ) twin pairs for genetics. A sensitivity analysis for asthma was performed in the STR by selecting the type of antibiotic (respiratory or urinary tract infection/skin) to correct for confounding by indication due to respiratory infections.

Results

Early-life antibiotic use was associated with significant increased risk of asthma (NTR: adj OR = 1.35, 95% CI = 1.27-1.38 and STR: adj OR = 1.45, 95% CI = 1.34-1.56) and eczema (NTR: adj OR = 1.11, 95% CI 1.06-1.16 and STR: adj OR = 1.07, 95% CI = 1.01-1.14) in unmatched analyses. The twin analyses for both MZ and DZ twin pairs showed similar results in both cohorts of increased risk of asthma, but not significant for eczema. When we selected antibiotics prescribed for urinary tract or skin infections and corrected for respiratory antibiotics, the risk for asthma attenuated (STR: adj OR = 1.02, 95% CI = 0.88-1.17).

Conclusion

Our results suggest that the association between early-life antibiotic use and asthma may be confounded by indication that is respiratory infections. The relationship between early-life antibiotics use and eczema may be confounded by shared familial environment and genetic factors. ■

Zie voor literatuurreferenties: NPFO.nl.