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Pharmacokinetic drug-drug interactions in the intensive care unit — single-centre experience and literature review

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Abstract

Background: Drug-drug interactions constitute a serious health hazard in everyday clinical practice in critically ill patients. Drug-drug interactions may be pharmacokinetic or pharmacodynamic in their nature. We aimed to investigate the quantity and quality of possible drug-drug interactions, and their possible side effects in intensive care unit patients in a 12-month period.

Methods: This retrospective study covered data on pharmacological treatment of 43 consecutive patients (11 females, 32 males) aged 62 ± 15 years, hospitalized between January 2015 and February 2016. Pharmacokinetic DDIs were identified and graded. Only severe and clinically important drug-drug interactions were subjected for further analysis.

Results: Median baseline SAPS III was 53 (IQR 38–67) points. Median intensive care unit stay was 12 (6–25) days. Subjects were treated with a median number of 22 (12–27) drugs. We identified 27 (16–41) possible drug-drug interactions per patient, including 3 (1–7) drug-drug interactions of a severe grade. The total number of severe and clinically important drug-drug interactions was 253 of which 227 were analyzed in detail. No possible side-effects of drug-drug interactions were identified.

Conclusions: DDIs as well as their side-effects are challenging regarding their precise evaluation, especially due to the need for multidrug treatment in critically ill patients. Concentration-controlled therapy should be recommended, especially for treatment with vancomycin, digoxin and valproate. Pantoprazole should be a proton pump-inhibitor of choice. Drug dose modification is necessary in combined treatment with fluconazole and amiodarone or rifampicin. From a clinical point of view, the most important impact of drug-drug interactions is on antibiotic treatment effectiveness, especially with meropenem when valproate is also prescribed.

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Key words: drug-drug interactions; pharmacokinetics; intensive care unit

Adverse drug effects (ADEs) are a significant medical and economic problem. ADEs that can be largely anticipated and counteracted are drug-drug interactions (DDIs) [1]. DDIs are either pharmacokinetic or pharmacodynamic in nature.

A pharmacokinetic drug interaction occurs when the change involves processes of absorption, transport, distribution, protein binding, transformation or excretion. Such interactions can be quantified. Pharmacokinetic interactions most commonly occur via acting on microsomal hepatic enzymes (cytochrome P-450 [CYP450] isoenzymes). The other mechanisms involve acting on phase II reactions (e.g. conjugation with glucuronic acid), affecting P-glycoprotein or displacing drugs from plasma protein-binding sites (e.g. albumins).

Pharmacotherapy in the intensive care unit (ICU) is multi-faceted, which is usually associated with the administration of multiple drugs [2]. The risk of potential DDIs increases with an increase in the number of drugs used [3].

The aim of the present study was to analyse the occurrence of pharmacokinetic DDIs, their severity and potential clinical consequences in critically ill patients treated in ICU.

METHODS

This retrospective analysis involved medical records of 43 consecutive patients hospitalised in one ICU between January 2015 and February 2016. An interaction was defined and classified according to Stockley's Drug Interactions' guidelines [4]. According to their severity, DDIs were divided into:

— severe — of high clinical relevance: drugs have to be used with great caution or their combinations should be avoided and the risks can exceed the benefits; the interaction can endanger health and life or require decisive clinical interventions;
— medium — of moderate clinical relevance; drugs should be used with caution, monitoring of the concentrations or effects of drugs, as well as dose modifications may be needed;
— minor — of slight clinical relevance; the interaction can be relevant when the other interactions or concomitant diseases accumulate, or when it is rare.

Only medium and severe potential DDIs (pDDIs) were analysed in detail, once deliberate interactions (e.g. the additivity of the hypotensive effect of thiazides and angiotensin convertase inhibitors), evident interactions (resulting from the mechanism of drug action), or those eliminated by standard ICU monitoring of patients were subtracted.

Descriptive statistics were applied. Quantitative variables were expressed as the median and interquartile range (IQR). Qualitative variables were presented as the absolute value and percentage.

RESULTS AND DISCUSSION

CHARACTERISTICS OF PATIENTS AND OCCURRENCE OF DDIS

The study group consisted of 11 women and 32 men aged 62 ± 15 (median 62) years. The baseline SAPS III score was 53 (IQR 38–67). The median duration of ICU treatment was 12 (IQR 6–25) days.

The patients received 22 (IQR 17–27) various drugs, 16 of which (IQR 13-19) were administered simultaneously. In total, 27 (IQR 16–41) DDIs were identified in each patient during the entire stay, including 4 (IQR 2–6) slight, 20 (IQR 10–31) medium and 3 (IQR 1–7) severe DDIs. After subtracting deliberate interactions, those which were evident and those eliminated by standard ICU monitoring of patients, there were 11 (IQR 7–16) interactions per patient. In total, 1,442 pDDIs were observed, including 253 pharmacokinetic ones, 227 of which were analysed in detail.

AMIODARONE

Amiodarone was the drug most commonly inducing pDDIs (n = 49), which usually concerned possible increases in the concentration of digoxin (n = 9), fentanyl (n = 7) and theophylline (n = 4). In single cases, interactions with lidocaine, statin, loperamide, levothyroxine, budesonide, sildenafil and lercanidipine were identified. Possible decreases in the concentration of clopidogrel were found in 6 cases.

In 4 cases, potential fluconasole-induced increases in the area under the curve (AUC) of amiodarone were observed. This interaction is all the more important as both drugs can lengthen the QT interval (thus the interaction is both pharmacokinetic and pharmacodynamic). In the available literature, itraconazole-induced increases in the concentration of amiodarone have been better described. As itraconazole more strongly inhibits cytochrome P450 enzymes, the probability of emergence of this interaction is higher when fluconazole is administered in a dose > 200 mg day $^{-1}$ [5]. At such doses, cases of sudden cardiac death have been reported [6]. It is worth noticing, however, that the growing number of reports emphasize the positive effect of interaction of the above drugs, which increases the activity of fluconasole against resistant fungal strains due to amiodarone-related inhibition of an antibiotic efflux pump by fungal cells [7, 8].

In single cases, amiodarone was administered with lidocaine, which could be associated with increased concentration of lidocaine due to decreased clearance by about 20% as a result of the inhibition of lidocaine metabolism by amiodarone, mediated by CYP3A4. Moreover, single cases of enhanced inhibition of the sinoatrial node activity have been reported [9, 10].

The interaction of amiodarone with loperamide does not seem particularly relevant in the ICU setting. As an inhibitor of P-glycoprotein and CYP3A4, amiodarone is likely to increase the concentration of loperamide in the blood and brain, which can be important in cases of the accumulative use of other opioids or the administration of high doses of loperamide (e.g. in cases of accidental or intentional overdose) [11].

Since sildenafil is metabolised by CYP3A4, its concentration can increase when administered with amiodarone, which in turn can favour the development of adverse effects of sildenafil, potentially necessitating a dose reduction [12].

Budesonide undergoes the first-pass effect and is metabolised by CYP3A4. Although amiodarone is not a potent inhibitor of this enzyme, cases of Cushing`s syndrome have occurred due to simultaneous administration of both drugs [13].

Amiodarone acts on levothyroxine in two ways. On the one hand, it inhibits convertase of thyroxin to triiodothyronine and reuptake of both molecules, which is likely to induce hypothyroidism. On the other hand, amiodarone contains substantial amounts of iodine in its molecule, which is liberated during metabolism and may lead to hyperthyroidism. Therefore, thyroid activity should be monitored more frequently when both drugs are administered [14, 15].

Due to CYP34 metabolism, the concentration of atrovasterol can increase during simultaneous administration with amiodarone, which is likely to result in hepatocyte damage and rhabdomyolysis. Therefore, a reduction in the statin dose to the lowest effective level is recommended, guided by lipidogram readings [16].

As the concentration of lercanidipine can increase during the administration of CYP3A4 inhibitors (for ketoconazole, a 15-fold increase was noted), during the administration of amiodarone a dose reduction may be required [17].

BENZODIAZEPINES

Potential DDIs with benzodiazepines (BDs) were recorded in 43 cases, most commonly with omperazole (n = 20), fluconazole (n = 9), theophylline (n = 6); single pDDIs were observed with statins, verapamil, isoniazids, rimfampicine and glucocorticosteroids (GCSs).

Omperazole increases concentrations of BDs metabolised via oxidation; the best known effect concerns diazepam and triazolam. It may be necessary to reduce the dose of BD [18] although the simplest and cheapest way to counteract this DDI (as well as many others) is to replace omperazole with pantoprazole.

Clinically relevant interactions occur when BDs are co-administered with azole antifungal antibiotics. For instance, ketoconazole increases the concentration of triazolam 22-fold, of midazolam — 10-fold and of alprazolam — 4-fold. Fluconazole induces slighter increases in concentrations of BDs, which is still clinically relevant at high doses (at least 200 mg daily). Such increases may deepen sedation and enhance ECG changes caused by BDs. When azole antifungal drugs have to be administered and the action of BD is found to be too strong, the dose of BD may be reduced or the azole antifungal drug may be replaced with terbinafine [19–22].

Theophylline reduces concentrations of BDs in the blood [23] and antagonises their action. Antagonism most likely involves inhibition competitive to adenosine bonds in the central nervous system (CNS) [24]. This interaction is of poor clinical relevance; however, some cases of reversal of diazepam-induced sedation following the administration of aminophylline [25], as well as the abolition of the effects of midazolam after the administration of theophylline have been reported [26].

Valproic acid can induce even a two-fold increase in the concentration of diazepam [27, 28]. When used simultaneously with clonazepam, its clearance can increase by 14% while the clearance of valproate can decrease by 18% [29]. In cases of co-administration with lorazepam, the concentration time of lorazepam was found to increase by 20% and the maximum concentration by 8%; nevertheless, this had no significant impact on the therapeutic effect [30]. The other BDs do not react with valproic acid and may be used provided that clinical efficacy is maintained.

DIGOXIN

The pharmacokinetic DDIs affecting the blood concentration of digoxin developed in 38 cases, most commonly in correlation with amiodarone (n = 9), omperazole (n = 8), BDs (n = 6) and in single cases with trimethoprim, spironolactone, aspirin and captopril. The concentration of digoxin was likely to decrease during simultaneous administration with metoclopramide (n = 5), as well as salbutamol and sulfasalazine.

An increase in the concentration of digoxin is extremely dangerous. Digoxin is a drug of a narrow therapeutic index. According to the summary of product characteristics, its therapeutic concentration is 1–2 ng mL^{-1}; however, according to the *Digitalis Investigation Group* this concentration is lower — from 0.5 ng mL^{-1} (0.64 nmol L^{-1}) to 1.0 ng mL^{-1} (1.28 nanomol L^{-1}). At the concentration > 3 ng mL^{-1}, the symptoms of intoxication are observed in most cases. The risk factors of digoxin intoxication include as follows: advanced age; hypokalaemia; hypomagnesaemia; hypercalcaemia; alkalosis; insufficiency of coronary vessels; myocarditis; hypoxia; pulmonary heart; reduced mass of skeletal muscles (e.g. during cachexia); and thyroid failure or kidney failure [31, 32]. Thus, patients treated in ICUs are particularly susceptible to drug toxicity. Consequently, the concentration of digoxin is routinely monitored in patients in the Silesian Centre for Heart Diseases.

The administration of amiodarone to a patient receiving digoxin is likely to be associated with an increase in the concentration of digoxin by 75% to 158 % via inhibiting the excretion of digoxin and reducing the volume of distribution [33]. The likely cause is the inhibition of P-glycoprotein activity by amiodarone [34]. During the use of amiodarone, the dose of digoxin should be reduced by 30–50% [35]. Further dose reductions are possible once the blood digoxin concentration has been checked. This interaction is one of the best known, and occurs in the majority of patients, with the effects being visible from several days to about 4 weeks after the concomitant administration of drugs [36].

Simultaneous use of digoxin with a proton pump inhibitor, especially omperazole, is associated with an increase in the concentration of digitalis glycoside by about 10–30% [37]. However, one case of a 3-fold increase has also been reported [38]. The above-mentioned changes are most likely to result from P-glycoprotein inhibition [39]. The effect is not the same for all proton pump inhibitors (PPIs) and seems least expressed for pantoprazole [40].

Alprazolam may cause even a three-fold increase in the concentration of digoxin [41]. Among the other BDs, only diazepam was associated with a moderate increase in digoxin concentration [42].

An increase in the concentration of digoxin by 22–34% has been demonstrated during its simultaneous use with trimethoprim, although only in the elderly [43].

Concomitant administration of digoxin and spironolactone may be associated with a reduction in clearance by about 25% and an increase in concentration by 20%; in one case a 4-fold increase was noted [44]. Additionally, it should be taken into account that spironolactone and its metabolite canrenone can falsely lower the results of digoxin concentration determinations carried out with certain methods (e.g. radioimmunoassay) [45]. In such cases, the methods based on chemiluminescence are the safest [46].

The interaction of acetylsalicylic acid with digoxin seems relevant only when the former is administered in doses of 1500 mg per day. In such cases, its concentration was found to be increased by 49% [47]. The use of antiaggregative doses is safe.

Interactions with captopril have been described as clinically irrelevant. Increases in the concentration of digoxin by 21% [48], 30% [49] and even 60% [50] have been reported. It is worth stressing that patients developing such changes had kidney failure and used diuretics.

In the material analysed, each of 10 patients receiving digoxin was also administered at least 2 drugs that may cause the above-mentioned interactions; in 5 patients, 3 drugs were used; in 2 patients - 4 drugs; and in another 2 patients - 6 drugs. With such combinations, even seemingly less-relevant interactions become important and it is extremely difficult to predict the digoxin concentration without its monitoring.

The combinations which may reduce blood digoxin concentrations were rarer and had lesser clinical relevance. For instance, metoclopramide can reduce the blood digoxin concentration by 27%, yet only when used orally [51]. A case of unclear pharmacodynamic interaction has been described , namely that regarding bradycardia and asystole, induced during simultaneous use of these drugs. Of note is that the concentration of digoxin did not exceed 1 ng mL^{-1} while the symptoms subsided after the withdrawal of both drugs [52]. In cases of simultaneous administration of an oral form of digoxin and sulfasalazine, the concentration of the former can decrease even by 50%, depending on the dose of sulfasalazine [53]. In cases of concomitant use with salbutamol, the interaction is confirmed only when a betamimetic is taken orally in a dose of 3–4 mg. In such cases, the permeation of digoxin to the skeletal muscles most likely increases [54]. By affecting the blood concentration of potassium, salbutamol can simultaneously induce digoxin toxicity.

THEOPHYLLINE

The concentration of theophylline can be affected by amiodarone (n = 4), fluconasole (n = 3), pentoxifylline (n = 3), ciprofloxacin (n = 3) and, in single cases, also by carvedilol, metroprolol, verapamil, furosemide and omperazole.

Theophylline, like digoxin, is a drug of a narrow therapeutic index. Its recommended concentration in blood is 10 to 20 μg mL^{-1} (56 to 112 μmol L^{-1}); above this value, the symptoms of toxicity are likely to develop (vomiting, seizures, coma, tachycardia, hypotension, tachypnoea, hyperglycaemia, metabolic acidosis, albuminuria. haematuria, hypocalcaemia). The drug dose should be calculated based on the fat free mass index. Monitoring of drug concentration in blood is recommended in each case; blood is sampled prior to each administration of the maintenance dose (after 12 h), which, however, was not feasible in our ICU. It should be remembered that caffeine and paracetamol can falsify the results of determinations carried out using radioimmunoassays and spectrophotometric methods [55]. In our study group, 10 out of 11 patients receiving theophylline were also administered paracetamol.

The interaction with amiodarone developed in one case while the concentration of theophylline doubled following the administration of amiodarone (an increase from 16.8 mg L^{-1} to 35 mg L^{-1}). This phenomenon may have been associated with the effects of amiodarone on thyroid function [56]. Moreover, amiodarone is an inhibitor of CYP1A2, whose substrate is theophylline [57]. The use of fluconazole, on the other hand, can be associated with the decreased clearance of theophylline by about 13–16% [58, 59]. One study in which theophylline was used with pentoxyllin has demonstrated an increase in theophylline concentration by 30% on average (ranging from an increase by 95% to a decrease by 13%) [60]. The effect of ciprofloxacin on the concentration of theophylline is much better documented and more significant; i.e. ciprofloxacin increases the concentration of theophylline by 17 to 113% [61, 62]. The mechanism of this interaction involves strong inhibition of CYP1A2 metabolising theophylline [53]. The importance of this issue is evidenced by the fact that 39 cases of interactions of these drugs were reported to the Food and Drug Administration (FDA) in 1991; three cases were fatal [63]. In such cases, the use of levofloxacin seems a safe alternative as this drug does not affect the metabolism of theophylline [64].

Verapamil can decrease the clearance of theophylline by 8–23% and the effect is dose-dependent [65]. One of the drugs belonging to calcium channel inhibitors is nifedipine, which can reduce the concentration of theophylline by 50–64% [66], increase it [67] or have no effect on it [68]. Moreover, positive effects of combining this pair of drugs have been reported [69]. The data regarding the use of theophylline with furosemide are equally conflicting. Although according to one study, the drug reduced the concentration of theophylline by 41% [70], in another study a 21% decrease was reported [71], while in yet another study, no changes in the concentration were observed, despite reduced clearance [72].

The administration of non-selective β-blockers (e.g. carvedilol, propranolol) and theophylline is contraindicated, mainly due to pharmacological antagonism (contraction of bronchial smooth muscles). This effect can also be present when cardio-selective drugs from this group are used (e.g. metoprolol), although it occurs more rarely and at higher doses [73]. The antagonism mentioned above was used for treating toxic effects of theophylline on the cardiovascular system and in cases of theophylline overdose, via the use of propranolol [74] and esmolol [75]. On the other hand, the administration of propranolol was found likely to be associated with a decrease in clearance by 37% while the use of metoprolol could result in a reduction by 11% (however, in the latter case, only in the group of tobacco smokers) [76]. Considering the above, there may be a situation in which the concentration of theophylline increases, its bronchodilative effect weakens while, simultaneously, cardiovascular toxicity intensifies.

The interactions of theophylline with omeprazole do not occur or are irrelevant, except for two cases, namely when theophylline is used in the form of modified-release tablets [77] or when the concentration of omperazole is high, e.g. when the patient is a weak metabolizer of CYP2C19 [78]. Fluconazole can cause even a 6-fold increase in the concentration of omeprazole. Omeprazole is an inducer of CYP1A2, which can accelerate theophylline metabolism.

The kinetics of theophylline is affected by thyroid function – as in hypothyroidism drug accumulation can be expected, levothyroxine can reduce the concentration of theophylline [79]. The assessment of pDDI relevance in the analysed material is complicated by the fact that just 2 patients developed only one episode of pDDI affecting the kinetics of theophylline. In 4 cases, patients received between 2 and 3 drugs**.** In one patient, the interactions of theophylline could have been affected by as many as 6 drugs.

FLUCONAZOLE

This drug was capable of increasing the concentration of amiodarone (n = 7), glucocorticosteroids (n = 4), zopiclone (n = 3), omeprazole (n = 3), as well as amlodipine, loperamide and cyclosporine.

Fluconazole is both a potent inhibitor of CYP2C9 and a moderate inhibitor of CYP3A4 (inducing a more than two-fold increase in concentrations of substrates). The inhibition of the former means that the drug significantly (more than 5 times) increases concentrations of substances that are substrates of this subtype of cytochrome, e.g. the majority of non-steroidal anti-inflammatory drugs, oral anti-diabetic drugs but also torsemide, warfarin and valproic acid. About 50% of the drugs used are substrates of CYP3A4; those relevant from the ICU point of view include the following: macrolides (except for azithromycin); BDs; cyclosporine; calcium channel antagonists (amlodipine, diltiazem, nitredypine, verapamil, lercanidipine); statins (except for rosuvastatin); carbamazepine; glucocorticosteroids (dexamethasone); fentanyl; haloperidol; lidocaine; ondansetron; propranolol; quetiapine; sildenafil or zolpidem [80].

Due to the effects on CYP2C19, the concentration of omeprazole increases markedly (ranging from 2- to 6-fold) [81]. These effects are slighter but also relevant for pantoprazole (clearance reduced to 66%) [82]. Since proton pump inhibitors are well tolerated and induce few adverse reactions after a short-term administration (and are also dose-dependent), this phenomenon seems important mainly in the context of pharmacokinetic interactions of this group of drugs. The other substrates of CYP2C19 are diazepam, clopidogrel and others.

FENTANYL

The most common pDDI in this group was an increase in the concentration of fentanyl resulting from the use of amiodarone (n = 7) and fluconazole (n = 2), and a decrease in the case of dexamethasone (n = 1).

Both the interactions with amiodarone and fluconazole result from the inhibition of CYP3A4, whose substrate is fentanyl. Fluconazole can reduce the clearance of fentanyl by 16% [83]. The literature has reported a fatal case in which the concentration of fentanyl used as a transdermal system increased to a toxic value and was accompanied by a high concentration of fluconazole. In the case of amiodarone, a pharmacodynamic reaction additionally occurs: enhanced cardiotoxicity (bradycardia, hypotension, myocardial depression) [85].

Since glucocorticosteroids induce CYP3A4, the concentration of fentanyl may decrease during their simultaneous use [86].

CIPROFLOXACIN

The most common pDDIs of ciprofloxacin were potential increases in the concentration of theophylline (n = 3) and zopiclone (n = 2), as well as of sildenafil (n = 2), pentoxifylline (n = 1) and simvastatin (n = 1).

Ciprofloxacin is a potent inducer of CYP1A2, which explains the interactions with theophylline. Of note is that the other drugs metabolised by this isoenzyme are haloperidol, ondansetron, verapamil and amitriptyalin [87]. The remaining interactions are explained by CYP3A4 inhibition [88].

The clinically relevant interactions of zopiclone have been demonstrated only with the simultaneous administration of a potent CYP3A4 inhibitor (e.g. clarithromycin, itraconazole) [89]; however, they can also be expected in the case of weaker inhibitors, such as CYP3A4**,** when other drugs inhibiting this isoenzyme are used (e.g. fluconazole,

verapamil, amiodarone), or in elderly patients, and those with impaired liver function and chronic respiratory failure. Thus, a dose reduction may be required in critically ill patients with multiple organ failure.

The interaction of ciprofloxacin can be considered in three aspects. The first one is pharmacokinetic — as ciprofloxacin induces a two-fold increase in AUC and C_{max} of sildenafil [90], a dose reduction should be considered. The second pharmacodynamic aspect concerns the fact that both drugs can lengthen the QT interval. The third aspect, which has been very poorly elucidated, involves reduced antibacterial efficacy of ciprofloxacin after the administration of phosphodiesterase type-5 inhibitors [91]. Although this effect has only been demonstrated *in vitro*, it should be considered when the treatment is ineffective.

The concentration of pentoxyllin can increase even by 60% and AUC by 15% during the simultaneous use of ciprofloxacin; therefore, it is suggested that the dose of pentoxyllin should be reduced by 50% [92].

Single reports concern rhabdomyolysis occurring when patients receiving statins are administered ciprofloxacin [93, 94].

VALPROIC ACID

The most significant and best studied pDDI of valproic acid is its reaction with carbapenems. A reduction in the concentration reached even 96% while, in many cases, a therapeutic concentration of valproic acid could not be obtained [95, 96]. Since interactions resulted in seizures, simultaneous administration of carbapenems is contraindicated. Moreover, it should be remembered that the concentration of valproate can drastically increase once a carbapenem is withdrawn [97]. When the DDI cannot be avoided, the blood concentration of valproic acid should be monitored; such monitoring was considered in our ICU.

Acetylsalicylic acid is known to displace valproic acid from blood protein-binding sites; however, the risk of DDI is substantial only when doses of acetylsalicylic acid are higher than those used for antiaggregative treatment [98].

The summaries of product characteristics of some foreign producers warn that valproic acid can increase the concentration of propofol in the blood by inhibiting glucoronisation in the liver [99]. The available study findings, however, seem to contradict this phenomenon [100].

PROTON PUMP INHIBITORS

The most relevant pDDI of this group of drugs is a decrease in the concentration of clopidogrel, with 4 cases present in the material analysed. Omeprazole can reduce AUC even by 45% and C_{max} by 49% [101]. The simplest way to counteract this interaction is to withdraw omeprazole or change to pantoprazole which induces a 14% decrease in AUC of clopidogrel [101], or to ranitidine.

The literature contains reports about minor interactions regarding the combination of omeprazole with warfarin [102], acetylsalicylic acid [103] or atorvastatin [104]. In such cases, the interaction can be relevant at a high concentration of omeprazole in the blood, i.e. when high doses are used (e.g. for the treatment of upper gastrointestinal tract haemorrhage), when the patient is a weak metabolizer of CYP2C19, or during the use of fluconazole. In each of the above cases, a safe alternative is pantoprazole.

VANCOMYCIN

Potential DDIs of vancomycin were noted in 6 cases and concerned the use of dobutamine (2), dopamine (3) and furosemide (5). In each case of the combined supply of glycopeptide and furosemide, the patient was treated with dobutamine or dopamine.

According to one retrospective study, dopamine, dobutamine and furosemide significantly affect the blood concentration of vancomycin. It has been demonstrated that their withdrawal (with the remaining pharmacokinetic parameters unaltered) was associated with an increase in stable concentration of vancomycin from 8.79 mg L^{-1} to 13.3 mg L^{-1}. Thus, the dose should have been reduced by 4.26 mg kg^{-1} day^{-1}. Most likely the drugs mentioned increase the clearance of vancomycin without affecting the serum concentration of creatinine [105]. Therefore, the only option of management in the cases of such a drug combination is treatment with blood vancomycin concentration monitoring.

RIFAMPICIN

Rifampicin may generate pDDIs with fluconazole and amiodarone in individual patients. Being an enzymatic inductor of numerous P-40 isoforms, p-acidic glycoprotein and glucoronisation_rifampicin induces many pDDIs. The mechanism of pDDIs with fluconasole remains unexplained as the drug is excreted in an unaltered form with urine. However, the changes involving a reduction in AUC and C_{max} of fluconazole by 22% and 17%, respectively have been demonstrated. In some cases, this was associated with a necessity to increase the dose of fluconazole [106].

As far as the interaction of rifampicin with amiodarone is concerned, only single reports have demonstrated the effect of a 40% reduction in serum concentration of amiodarone and the resultant need to double the dose of an antiarrhythmic drug, which in turn was associated with a sudden increase in the concentration of amiodarone and its metabolites after the withdrawal of rifampicin [107].

CLINICAL CONSEQUENCES OF INTERACTIONS

In none of the cases, could the cause-and-effect relationship between pDDI and the patient`s condition have been documented. Unfortunately, in critically ill patients

with multiple organ failure, it is difficult to evaluate in real terms the clinical consequences of pharmacokinetic drug-drug interactions, which is the major limitation of our study.

CONCLUSIONS

1. Drug-drug interactions in critically ill patients are a complex problem, one which is difficult to evaluate as the treatment is often accompanied by polypragmasia. Moreover, the evaluation of clinical effects of interactions is questionable as many of them may develop spontaneously during hospitalisation.
2. DDIs can often be monitored through well-designed drug concentration monitoring, which particularly concerns vancomycin, digoxin and valproic acid. Another way is to replace the drug inducing DDIs with another one of similar action, e.g. omeprazole with pantoprazole. In some cases, the dose of the drug has to be modified, e.g. during the simultaneous use of fluconazole, amiodarone or rifampicin.
3. From the clinical point of view, the possibility of DDI occurrence has to be considered in ICU patients, mainly during rational (effective) antibiotic therapy, as some DDIs suggest that treatment with one of the drugs, e.g. meropenem, should be withdrawn during treatment with valproic acid.

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