Supplementary material

Supplementary table 1. Clinical studies and case reports on interactions between antibacterials and antiseizure medications in paediatric patients

Class J. Anti-infectives	
Amikacin	**Case report:** A combination therapy of amikacin and meropenem lowered VPA plasma concentrations in one patient (1). ***Not informative:*** it can be supposed that this effect was caused by meropenem
Ciprofloxacin	**Clinical study:** Ciprofloxacin significantly increased Cmax, AUC and t½ while it decreased the CL and Vd of CBZ when given concurrently to eight healthy adult male volunteers (2). ***Concordant with drug compendia*** **Case reports:** Reports documented that ciprofloxacin reduces levels of PHT (3,4). ***Concordant with drug compendia*** An old patient with epilepsy and treated with PHT had seizure relapses after administration of ciprofloxacin eye drops (5). ***Concordant with drug compendia***
Clarithromycin (not present in Medscape)	**Clinical study:** In an overview of ten patients receiving CBZ (seven from the French national drug safety centre) alone or in combination with other drugs, administration of clarithromycin led to transitory CBZ overdosage (6). ***Concordant with drug compendia*** In an open-label, randomized, crossover study clarithromycin caused a statistically significant increase in midazolam concentrations compared to controls (7). ***Concordant with drug compendia*** In a study on healthy elderly volunteers treated with midazolam, oral, hepatic and intestinal availability of midazolam was significantly increased after clarithromycin administration (8). ***Concordant with drug compendia*** In a study on 16 heathy volunteers, in addition to the liver, the gut was shown to be a major site of interaction between oral midazolam and clarithromycin (9). ***Concordant with drug compendia*** **Review (10)** **Case reports:** In a patient receiving CBZ monotherapy, 10-day antibiotic treatment increased CBZ concentration despite concomitant CBZ dose reduction and doubled CBZ concentration/dose ratio. Concentration of the CBZ epoxide metabolite was reduced (11). ***Concordant with drug compendia*** One case of severe OXC toxicity after starting clarithromycin was reported in a patient with refractory epilepsy. Clarithromycin may inhibit the efflux proteins of the blood-brain barrier, which are thought to be over-expressed in drug-resistant patients (12). **Child** ***Discordance with drug compendia***
Chloramphenicol	**Case reports:** Concurrent administration of chloramphenicol and PB in six patients resulted in reduced peak and trough concentrations of chloramphenicol; concurrent administration of chloramphenicol and PHT resulted in an elevated mean peak serum concentration of chloramphenicol (13). **Infants and children** ***Discordance concerning the effect of PHT on chloramphenicol*** A patient is described who was treated with chloramphenicol for a ventriculojugular shunt infection. Subsequent addition of PHT and PB caused a significant decrease in chloramphenicol serum concentration and an increased clearance of the agent (14). **Child** ***Concordant with drug compendia*** A patient is reported who had primidone toxicity after starting treatment with chloramphenicol (15). ***Interaction not reported in the compendia***

	A case of PHT intoxication induced by chloramphenicol is described (16). ***Concordant with drug compendia*** **Review of clinical data** (17,18) **concordant with prediction**
Doxycycline	**Clinical studies:** In a clinical study, the mean half-life of doxycycline given to seven patients on long-term PHT treatment was 7.2 +/- 0.4 hours. In five patients on long-term CBZ treatment, the half-life was 8.4 +/- 1.4 hours. In four patients on combined PHT and CBZ treatment, the half-life was 7.4 +/- 0.7 hours. All these figures were significantly shorter than the mean half-life of 15.1 +/- 1.0 hours for doxycycline given alone to nine control patients. Therefore, at normal doses of doxycycline, it may not be possible to maintain the minimum inhibitory concentration necessary for proper bacteriostasis when coadministered with PHT or CBZ (19). ***Concordant with drug compendia*** In a cross-over study of five hospitalized patients, the half-life of doxycycline was significantly shortened after a 10-day treatment with phenobarbitone (20). ***Concordant with drug compendia***
Erythromycin	**Clinical studies:** In an open, cross-over study with 12 healthy subjects, erythromycin, but not azithromycin, caused a clinically significant increase in MDZ concentrations (21). ***Concordant with drug compendia*** A controlled two-way cross-over study in eight healthy volunteers revealed that clearance of oral CBZ was lower in the presence of erythromycin (22). ***Concordant with drug compendia*** A cross-over study on 8 healthy volunteers showed that OXC pharmacokinetics was not significantly influenced by erythromycin (23). ***Concordant with drug compendia*** An open-label, randomized, two-period, crossover study in patients with epilepsy showed that the pharmacokinetics of felbamate was not influenced by erythromycin coadministration (24). ***Concordant with drug compendia*** A randomised cross-over study conducted in eight healthy volunteers indicated that the intrinsic clearance of unbound PHT was unaffected by the concurrent administration of erythromycin (24). ***Concordant with drug compendia*** The effects of erythromycin on PHT were studied in eight healthy, volunteers in a crossover study. Erythromycin failed to significantly decrease mean PHT clearance (25). ***Concordant with drug compendia*** **Case reports:** Erythromycin increased VPA levels in a patient with epilepsy and bipolar disorder (27). ***Concordant with drug compendia*** A further case of erythromycin-induced CBZ toxicity (28). **Child** ***Concordant with drug compendia***
Carbapenems (Ertapenem Imipenem and cilastatin meropenem)	**Retrospective clinical studies:** In a 5-year retrospective study, VPA serum concentrations of 52 patients were found to be subtherapeutic in 90% of the subjects during treatment with carbapenem antibiotics (ertapenem, n=9, imipenem/cilastatin, n=17, and meropenem, n=26). The effect of ertapenem and meropenem on VPA was significantly greater than that of imipenem/cilastatin ($p<0.005$). The onset of this interaction occurred within 24 hours of carbapenem administration. Carbapenems reduced VPA serum concentration by approximately 60%. Ertapenem and meropenem had a greater effect than imipenem/cilastatin (29). VPA drug monitoring records from 381 patients treated with VPA and meropenem showed remarkable lower values of VPA levels in comparison with specimens from patients taking VPA without this agent. VPA levels recovered to a value before meropenem initiation, seven days after meropenem discontinuation (30) ***Children, adults and elderly*** Based on a retrospective evaluation of therapeutic drug monitoring reports, a decrease in the serum concentrations of VPA during concomitant use of carbapenem antibiotics was observed in 6 cases (31). In a retrospective study, all 39 patients treated simultaneously with VPA and meropenem had an average drop in VPA plasma concentrations of 66%. In 19 patients who had daily plasma concentration monitoring, the decrease occurred within 24 hours (32). ***Children and adults*** In a retrospective study of 28 children who simultaneously received treatment with VPA and carbapenem, 88% of VPA

	levels were below therapeutic range and 54.5% of patients had relapses of seizures after the introduction of this antibiotic (33). ***Children*** In a retrospective evaluation of data from 36 hospitalized patients, VPA mean plasma levels decreased from 50.8 to 9.9 mcg/ml following meropenem administration (34). Six critically ill VPA-treated patients who concurrently received meropenem (n=4), imipenem (n=1), or ertapenem (n=1) had VPA plasma levels decreases by 58%. All VPA concentrations measured during concurrent VPA-carbapenem treatment were below the lower boundary of therapeutic range and 5 patients experienced generalized seizures (35). In a retrospective analysis, 26 patients received concurrent treatment with VPA and meropenem and none of them maintained therapeutic serum levels of the antiseizure drug (36). ***Concordant with drug compendia*** **Case reports:** VPA levels were reduced by ertapenem but not by meropenem in one patient (37). One patient with epilepsy and treated with VPA presented seizures soon after ertapenem was added. VPA levels were 130 mcg/ml before ertapenem therapy and 70 mcg/ml and 10 mcg/ml during treatment with ertapenem (38). In two patients with epilepsy/status epilepticus undergoing treatment with VPA, ertapenem caused seizure relapses (39). In a patient who ingested a toxic VPA dose, meropenem was successfully used to shorten VPA half-life and absorption (40). Decreases of VPA serum levels by 90.8% and 93.5% were observed after starting concomitant administration of meropenem (41). A drop of VPA plasma levels was observed after starting meropenem treatment in one patient (42). In a patient treated with VPA for epilepsy, administration of meropenem reduced serum VPA concentrations and impaired the control of seizures, which failed to respond to intravenous supplementation of sodium VPA (43). An average decrease of 70% in serum levels of VPA due to concomitant use of VPA and carbapenem antibiotics was described in seven cases: panipenem (1 case), meropenem (3 cases), and imipenem (2 cases), and in one case both imipenem and meropenem (44). ***Adults and children*** The first reported case of interaction between VPA and meropenem (45). ***Child*** **Further cases in children** (46, 47, 48). Further cases in adults or the elderly (49,50.51,52,53). ***Concordant with drug compendia***
Gentamicin	**No clinical data**
Isoniazid	**Editorial:** A complex (both pharmacokinetic and pharmacodynamic) DDI between CBZ and isoniazid was described (54). ***Concordant with drug compendia*** **Clinical study:** The effect of simultaneous administration of isoniazid (300 mg/day) and PHT (300 mg/day) in 60 patients with tuberculous meningitis and seizures was evaluated. Plasma samples were analysed for isoniazid, acetylated-isoniazid and PHT levels. Slow acetylator phenotypes were associated with higher isoniazid plasma levels and lower acetylated-isoniazid plasma levels as compared to rapid acetylators; plasma PHT levels were significantly higher (above therapeutic range) in slow acetylators as compared to rapid acetylators (55). ***Concordant with drug compendia*** **Case reports:** Documented cases of DDIs between isoniazid and CBZ (56) and PHT (57). ***Concordant with drug compendia*** A patient is reported who was treated with PHT and isoniazid, and was a slow acetylator and developed PHT toxicity (58). ***Concordant with drug compendia*** A case with increased CBZ levels caused by isoniazid and cimetidine (59). ***Concordant with drug compendia***

	Cases with VPA overdoses and toxicity caused by isoniazid (60,61,62). ***Concordant with drug compendia*** A case of increased ETS levels caused by isoniazid is described (63). ***Interaction NOT reported in drug compendia***
Levofloxacin	**Clinical case report:** Two patients had a decrease in PHT caused by levofloxacin (64). ***Concordant with drug compendia***
Metronidazole	**Clinical studies:** In a randomised, placebo-controlled, cross-over study conducted in 10 healthy subjects, metronidazole had no effect on the pharmacokinetics of midazolam (65). ***Discordant with compendia*** In an open-label, parallel study, PHT (300 mg) was given to patients taking and not taking metronidazole. Compared with control, metronidazole treatment significantly prolonged half-life (23 versus 16 hours) and reduced clearance of PHT (66). ***Concordant with drug compendia*** In a study conducted of six Crohn's patients, PB induced the metabolism of metronidazole (67). **Case report:** A woman treated with CBZ (1000 mg/day) received metronidazole due to diverticulitis. A 60% increase in CBZ level and toxicity was observed soon after metronidazole treatment (68). ***Concordant with drug compendia***
Sulfamethoxazole and trimethoprim	**Clinical study:** In a population-based, nested case-control study, in old patients receiving PHT, treatment with sulfamethoxazole and trimethoprim was associated with a more than two-fold increase in PHT concentrations with a risk of toxicity (69). ***Concordant with drug compendia*** **Case report:** A documented case of interaction between PHT (concentration increased) and sulfamethoxazole and trimethoprim (70). ***Concordant with drug compendia***

Abbreviations: AIDS=acquired immune deficiency syndrome, ASM=antiseizure medication, AUC=area under the curve, CBZ=carbamazepine, DDI=drug-drug interaction, ETS=ethosuximide, HIV=human immunodeficiency virus, LTG=lamotrigine, OXC=oxcarbazepine, PB=phenobarbital, PHT=phenytoin, VPA=valproic acid.

Child/children: studies in which it was explicitly stated that DDI was observed in children.

Supplementary table 2. Clinical evidence of interaction between antimycotics and antiseizure medications in paediatric patients.

J02 Antimycotic drugs and drugs for treatment of tuberculosis	
Bedaquiline	**No clinical data**
Fluconazole	**Controlled studies:** Placebo-controlled, parallel study. PHT (200 mg) was given both in the presence and absence of fluconazole in 20 healthy male subjects. PHT dose was 200 mg orally and fluconazole dose was 200 mg/die. AUC of plasma PHT was 75% higher during fluconazole treatment (71). ***Concordant with drug compendia*** In a study conducted on 10 mechanically ventilated patients sedated with a stable midazolam infusion, fluconazole treatment was started and determined a significant increase in midazolam levels (72). ***Concordant with drug compendia*** **Case reports:** Fluconazole-induced symptomatic PHT toxicity was described in two cases (63). ***Concordant with drug compendia*** Fluconazole-induced PHT toxicity was reported in one case (74). ***Concordant with drug compendia*** A case of CBZ toxicity resulting from a drug interaction with fluconazole was reported (75). ***Concordant with drug compendia*** One patient had high CBZ serum concentrations during concomitant fluconazole administration (76). ***Concordant with drug compendia*** A case of fluconazole-induced CBZ toxicity was described (77). ***Concordant with drug compendia*** A patient taking CBZ for a bipolar disorder had toxic adverse effects caused by CBZ after the beginning of fluconazole therapy (78). ***Concordant with drug compendia***
Rifapentine	**No clinical data**
Rifampicine	**Case reports:** An old patient treated with PHT and PB was treated with rifampicin and ethambutol for pulmonary tuberculosis. Upon withdrawal of antimicrobials, an increase in PHT concentration was observed over the subsequent days, indicating a lack of induction of PHT metabolism (79). ***Concordant with drug compendia*** A significant decrease in the active metabolite of OXC was reported in one patient taking this drug after rifampicin administration (80). ***Interaction NOT predicted***
Voriconazole	**Clinical study:** An open-label study on 21 healthy volunteers investigated the effect of PHT (300 mg/day) on the pharmacokinetics of voriconazole (200 mg and 400 mg twice daily). PHT decreased the mean steady-state Cmax and AUC of voriconazole by approximately 50% and 70%, respectively. This effect was compensated by a doubling of voriconazole dose (81). ***Concordant with drug compendia*** **Randomized clinical study:** A double-blind study of 15 healthy volunteers investigated the effects of voriconazole (400 mg twice daily) on the pharmacokinetics of PHT (300 mg once daily). Voriconazole increased the mean steady-state Cmax and AUC of PHT by approximately 70% and 80%, respectively (81). ***Concordant with drug compendia*** **Clinical case report:** Three cases were described showing that a phenytoin-induced decrease in voriconazole concentration could not be compensated by doubling voriconazole dose in seriously ill patients, in contrast to that observed in healthy volunteers (82). ***Concordant with drug compendia***
Isoniazid	*see supplementary table 1*

Abbreviations: AIDS=acquired immune deficiency syndrome, ASM=antiseizure medication, AUC=area under the curve, CBZ=carbamazepine, DDI=drug-drug interaction, ETS=ethosuximide, HIV=human immunodeficiency virus, LTG=lamotrigine, OXC=oxcarbazepine, PB=phenobarbital, PHT=phenytoin, VPA=valproic acid.

Supplementary table 3. Clinical evidence of interactions between antiviral and antiseizure drugs in paediatric patients.

Class J. Antiviral drugs for systemic use	
Drug for HIV/AIDS	
Atazanavir/ritonavir Also used for COVID-19	**Clinical studies:** Atazanavir and dolutegravir concentrations significantly decreased in 11 HIV-positive patients treated with CBZ or OXC and antiretrovirals over at least 3 months, in comparison with values typically measured in HIV-infected patients not treated with antiseizure drugs (83). ***Mixed populations*** ***Concordant with drug compendia*** In 12 adult HIV-infected subjects treated with daily atazanavir (300 mg) and ritonavir (100 mg) for at least 4 weeks, minocycline and VPA coadministration resulted in decreased atazanavir exposure. However, there was no evidence that VPA mediated this effect (84). ***Not informative*** In a study conducted on 22 healthy volunteers, LTG was administered alone, with atazanavir or with atazanavir/ritonavir. Atazanavir alone did not significantly influence glucuronidation of LTG, while atazanavir/ritonavir resulted in moderately decreased exposure to LTG (85). ***Concordant with drug compendia*** **Case reports:** In one patient undergoing treatment with antiretroviral agents for HIV infection, novel anti-hepatitis C virus agents and CBZ required drug monitoring of plasma levels and complex changes in dose regimens (86). ***Concordant with drug compendia*** A toxic CBZ concentration was observed in one patient who concomitantly received ritonavir for HIV infection (87). ***Concordant with drug compendia***
Dolutegravir	Coadministration of CBZ (300 mg twice daily) and dolutegravir (50 mg once daily) decreased dolutegravir Cmax, AUC and Cmin by 33%, 49% and 73%, respectively (88). ***Concordant with drug compendia*** Treatment with VPA was associated with lower levels of dolutegravir (89). ***Interaction NOT predicted*** Eight patients with HIV inadvertently received OXC while receiving dolutegravir. In such patients, OXC did not adversely affect viral suppression (90). ***Prediction NOT confirmed*** **Case reports:** In one patient with HIV-infection, PB led to a remarkable reduction in plasma concentration of dolutegravir (91). ***Concordant with drug compendia***
Efavirenz	**Clinical studies:** A randomized, open label, cross-over study assessed the effect of efavirenz (600 mg) on the pharmacokinetics of CBZ (400 mg) and vice versa in 36 adult healthy subjects. Coadministration of CBZ and efavirenz significantly reduced the exposure to efavirenz and CBZ (92). ***Concordant with drug compendia*** VPA (250 mg twice daily) was administered to HIV-1 infected patients receiving, or not, efavirenz or lopinavir-ritonavir. Efavirenz or lopinavir/ritonavir did not significantly influence VPA levels (93)**.** ***Concordant with drug compendia*** **Case reports:** A bipolar patient with concomitant multidrug addiction presented with a decrease in VPA plasma levels of more than 50% shortly after antiretroviral therapy was initiated (94). ***Not informative*** A case is described in which a potential bidirectional interaction between PHT and efavirenz resulted in lower-than-expected efavirenz concentrations and elevated PHT levels (95). ***Concordant with drug compendia*** In one case report, efavirenz levels were not affected by OXC (96). ***Prediction NOT confirmed*** A drug interaction between efavirenz and PHT was reported (97).

	Concordant with drug compendia A case of CBZ toxicity after starting an antiretroviral treatment regimen including ritonavir and efavirenz was reported. A dose reduction of CBZ from 600 to 100 mg was required to achieve a therapeutic concentration. As efavirenz is a CYP3A4 inducer, CBZ toxicity was almost certainly caused by ritonavir (98). ***Concordant with drug compendia***
Etravirine	**Case report:** A case is reported in which a DDI between CLB and etravirine combination was associated with increased concentrations of CLB and its pharmacologically active metabolite, N-desmethylclobazam, with consequent neurotoxic symptoms (99). ***Concordant with drug compendia***
Indinavir	**Case reports:** A case of antiretroviral therapy failure after introduction of CBZ (200 mg/day) was reported (100). ***Concordant with drug compendia***
Lopinavir/ritonavir Also used in COVID-19	**Clinical studies:** In an open-label, randomized, pharmacokinetic study in healthy volunteers, concomitant lopinavir/ritonavir and PHT resulted in a 2-way drug interaction. PHT increased lopinavir clearance via CYP3A4 induction, which was not offset by the presence of low-dose ritonavir, and lopinavir/ritonavir increased PHT clearance via CYP2C9 induction (101). ***Concordant with drug compendia*** Twenty-four healthy subjects received LTG with subsequent addition of lopinavir/ritonavir. Lopinavir/ritonavir decreased the AUC of lamotrigine, probably by inducing glucuronidation. Dose increments of 200% were required to achieve concentrations similar to those with lamotrigine alone (102). ***Concordant with drug compendia*** A pharmacokinetic study on HIV-1 infected patients showed that efavirenz was not influenced by VPA coadministration while lopinavir concentrations tended to be higher when this drug was combined with VPA. VPA levels were not significantly influenced by efavirenz and lopinavir/ritonavir (93). ***Concordant with drug compendia*** Thirteen healthy volunteers received single 3-mg oral doses of midazolam in controlled conditions and during co-treatment with low-dose ritonavir. The AUC following oral midazolam was increased by a factor of 28.4, and reduced oral clearance to 4.2% of controls. ***Concordant with drug compendia*** **Case reports:** A patient was treated with VPA for bipolar disorder, and initiated a treatment with lopinavir/ritonavir, zidovudine, and lamivudine. Twenty-one days after starting antiretroviral treatment, he became increasingly manic and VPA concentrations decreased to 48% relative to previous measurements (104). It was suggested that ritonavir induced VPA glucuronidation. ***Concordant with drug compendia*** An HIV-positive male patient developed excessive drowsiness secondary to CBZ after introduction of antiretroviral regimen containing lopinavir/ritonavir. The CBZ serum concentration increased by 46% (105). ***Concordant with drug compendia***
Maraviroc	In a randomized, double-blind, placebo-controlled study conducted in healthy subjects, maraviroc showed no clinically relevant effects on the pharmacokinetics of midazolam (CYP3A4 substrate) (106). **Adults** ***Concordant with drug compendia***
Tipranavir	Coadministration with CBZ (200 mg twice daily) decreased tipranavir Cmin by 61% when compared to controls (88**)**. ***Concordant with drug compendia*** **Case report:** A 49-year-old man with AIDS and epilepsy was treated with PB (100 mg daily). Previous multiple treatment failures led to a new regimen with abacavir, didanosine, tipranavir-ritonavir (500/200 mg twice daily) and enfuvirtide. Four weeks later, the patient had an episode of seizures and PB levels decreased (107). ***Not informative***
Zidovudine	**Clinical study:** Serum PHT concentrations were investigated in 21 patients with AIDS and 557 control subjects during PHT therapy. Total PHT concentrations were significantly lower in patients with AIDS than in the reference population, although PHT doses were significantly higher in AIDS patients (108). ***Mixed population*** ***Concordant with drug compendia*** VPA was added to zidovudine in six patients infected with HIV. The oral clearance of zidovudine decreased and the plasma AUC increased two-fold (109). ***Concordant with drug compendia***

	Case report: Severe anaemia due to zidovudine, caused by a pharmacokinetic interaction with VPA, was reported in two patients (110,111). ***Concordant with drug compendia***

Abbreviations: AIDS=acquired immune deficiency syndrome, ASM=antiseizure medication, AUC=area under the curve, CBZ=carbamazepine, DDI=drug-drug interaction, ETS=ethosuximide, HIV=human immunodeficiency virus, LTG=lamotrigine, OXC=oxcarbazepine, PB=phenobarbital, PHT=phenytoin, VPA=valproic acid.

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