CORRESPONDENCE

Drug Interactions—Principles, Examples and Clinical Consequences

by Prof. Dr. med. Dr. rer. nat. Ingolf Cascorbi in volume 33–34/2012

Additional Important Drug Interactions

Considerations should also focus on seriously ill or at-risk patients, such as patients in intensive care or receiving anticancer treatment, for whom state-of-the-art drug treatment is the basis of prolonging life or leading to improvement.

What might be important in this context—and was not discussed in the current article—is a possible reduction or loss of drug effectiveness due to an inadequate administration interval—for example, between the administration of dexamethasone and temozolomide in patients with brain tumors. Both medications are usually given under clinical conditions once a day, simultaneously, in the morning. Maximum blood concentrations after administration of both drugs are reached after 0.5–2 hours. Dexamethasone has a membrane-stabilizing and strongly sealing effect on the blood-brain barrier (1, 2), so that the low neurological bioavailability of temozolomide, reportedly 30%, is predictably reduced and may contribute to an undesirable treatment failure. On the basis of the pharmacokinetic properties of both medications it would be advisable to postpone the administration of dexamethasone to, for example, 4–6 hours after temozolomide.

A change in strength of efficacy as a result of displacement from the plasma protein binding was not mentioned. This is also true for dexamethasone, strongly bound to albumin, in interaction with other medications that are also bound to plasma protein.

Lithium with its pronounced interaction profile should have been included among the antidepressants/antipsychotics (Lecture by K Lehmann on interactions of lithium, 2nd annual meeting of the ANPT (Working group of neuropharmacology and toxicology) Dresden, 15–18 September 1993).

Interactions of drugs with a narrow therapeutic range, including their clinically relevant consequences, are generally of particular importance and should be addressed explicitly.

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In Reply:

The considerations of the article on drug interactions apply not only to patients with multimorbidities but also in general.

I agree that the consequences of pharmacokinetic interactions are more pronounced especially among drugs with a narrow therapeutic range. Lithium is a further typical example in this context.

The correspondent's statement that dexamethasone "seals" the blood-brain barrier and thus inhibits the penetration of the alkylant temozolomide, which is indicated for glioblastoma tumors, lacks evidence. Möhnle et al. discuss non-genomic effects of high-dose dexamethasone on plasma membranes, which would lead to inhibition of the Na⁺- and K⁺-fluxes, rather than pharmacokinetic interactions with temozolomide (1). A reduction of the bioavailability of temozolomide in the central nervous system in presence of glucocorticoids has not been described. However, there are in-vitro indications of a pharmacodynamic interaction, albeit one whose effects are negative: it seems that dexamethasone protects human glioblastoma cells from temozolomide induced apoptosis (2, 3).

There are certainly many specific examples that provide an impetus for further discussion; however, our CME article aimed to provide a systematic overview of pharmacokinetic interactions in principle and, in addition, to draw attention to some examples of typical pharmacodynamic interactions that should be considered during therapy.

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Conflict of interest statement

The authors of all contributions declare that no conflict of interest exists.