

Dexamethasone/phenytoin interactions: neurooncological concerns

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The recent "Letter to the Editor" of Debrunner et al. in this journal reporting a falsely positive dexamethasone suppression test under concomitant phenytoin medication adds to the knowledge of clinically relevant effects of dexamethasone/phenytoin interactions [1].

From a neurooncological and intensive care viewpoint too, the dexamethasone/phenytoin interaction merits special consideration.

Dexamethasone and phenytoin are frequently given together as a standard therapy for patients with newly detected primary or secondary brain tumours, and phenytoin is often administered purely prophylactically, i.e. even when the patient did not experience seizures yet.

Phenytoin uniformly decreases the levels of dexamethasone, accelerating its metabolism through induction of hepatic microsomal enzymes [2]. On the other hand, both increased [3] and lowered [4-7] levels of phenytoin were observed under comedication with dexamethasone (in our experience, decreased phenytoin levels outweigh by far). The exact mechanisms for these conflicting phenomena remain to be elucidated, but increased levels are attributed to competition on protein binding, whereas decreased levels may be caused upon induction of hepatic metabolism.

Phenytoin and dexamethasone will mutually lower the efficacy of the other drug, resulting in the need to step up the doses of both medications (in the case of phenytoin up to 600-1000 mg/d). As important clinical consequences, first, it will be next to impossible to predict the levels of phenytoin in an individual patient taking dexamethasone and, consequently, careful monitoring of phenytoin levels is highly recommended. Second, tapering of dexamethasone after successful control of the tumour-associated brain oedema has to be paralleled by a reduction of phenytoin according to close drug level monitoring [5].

Failure to adjust the phenytoin dosage may lead to serious intoxication, accentuated by the particular pharmacokinetics of this drug. The acute neurological signs of phenytoin intoxication (somnia, ataxia, nystagmus) can simulate tumour progression and incapacitate the patient for a longer time. Acute phenytoin intoxication may cause severe skin reactions and, rarely, persisting and debilitating cerebellar atrophy [8, 9].

Additionally, from the neurooncological viewpoint, phenytoin and other inducing antiepileptic agents have been found to lower the efficacy of antineoplastic treatments [10, 11].

Phenytoin further interferes with coumarins, which are often given in view of the secretion of procoagulatory factors by brain tumours.

In conclusion, the combination of dexamethasone and phenytoin should be avoided in patients with brain tumours. In this context it is important to note that purely prophylactic antiepileptic medication in patients with newly diagnosed brain tumours lacks evidence of efficacy and is not recommended according to the report of the Quality Standards Subcommittee of the American Academy of Neurology [12]. In cases of brain tumour-related seizures where antiepileptic therapy is mandatory, drugs with fewer side effects and with no relevant induction of hepatic enzyme systems (i.e. valproic acid, gabapentin, levetiracetam) should be preferred.

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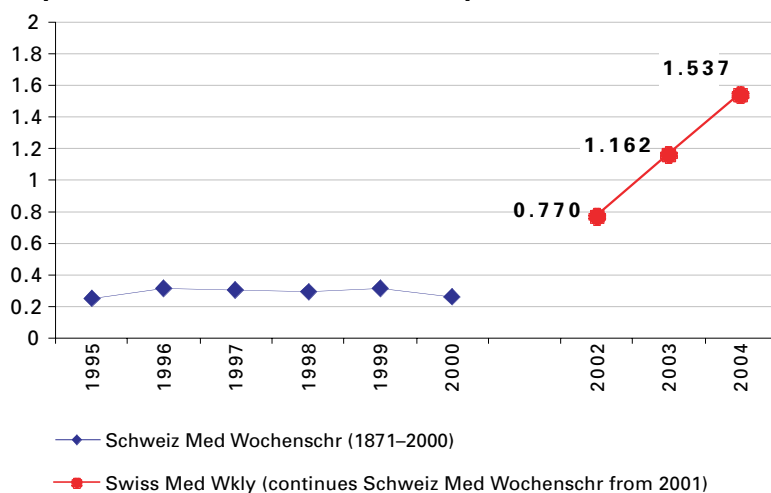
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