Zopiclone: some remarks on pharmacokinetics and pharmacodynamics

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Although the reported case of Kuntze et al. [1] provides some evidence that zopiclone has a favourable therapeutic index, some important data are lacking. Pharmacokinetic, pharmacodynamic and pharmacogenetic issues cannot be ignored in this context. Unfortunately, the plasma concentration of zopiclone (or urine metabolites) was not measured.

Zopiclone is a widely prescribed, non-benzodiazepine hypnotic. The duration of its pharmacological effect and the occurrence of adverse effects are mainly dependent on its biological half-life and clearance. In humans, zopiclone elimination is mainly related to its hepatic clearance as only 5% of the drug is excreted unchanged in the urine [2]. Indeed, zopiclone is extensively metabolised by the human liver into two major metabolites: N-oxidezopiclone, which retains a low pharmacological inactivity; and N-desmethylzopiclone, which is pharmacologically inactive [3]. The enzymes involved in zopiclone metabolism have not yet been identified [2], but cytochrome P-450 isoforms may be suspected as some drug interactions in humans with cytochrome P-450 inhibitors or inducers have been reported [4–6]. The severity of beneficial or adverse drug effects may be influenced by the possible administration of such potential cytochrome P-450 inhibitors or inducers.

Secondly, zopiclone is rapidly and widely distributed in body tissues including the brain [7]. In animal experiments, the highest accumulation is in muscle, lung, liver, fat tissue and kidney [8]. From this point of view, one might suggest that an increased body mass index may have some influence on the incidence of potential adverse effects of zopiclone. In addition, the pharmacokinetics of zopiclone is altered by aging and influenced by hepatic function [7], both of which may be specific patient characteristics in the report of Kuntze et al. [1], as no exact information on hepatic function is given.

Thirdly, the lack of clinically significant adverse effects of zopiclone may be explained by its unique pharmacokinetic (rapid elimination half-life) and pharmacodynamic (low affinity and specific binding profile to various subunits of the GABA(A) receptors) profiles [9]. In order to discuss the effects of overdosage of zopiclone, the plasma level of the substance or their metabolites in the urine must be quantified. This can be done in the case of zopiclone [7, 10, 11]. For this reason, the assumption of an approximate value of a plasma level of zopiclone in the present case report may limit specific discussion from the pharmacological point of view.

In conclusion, adverse effects of zopiclone may occur under single-dose conditions or at steady-state. The pharmacodynamic consequences may or may not closely follow pharmacokinetic changes. Temporal relationship between the administration of the drug and elevated plasma concentrations may be important in determining the extent and the specificity of possible adverse effects.

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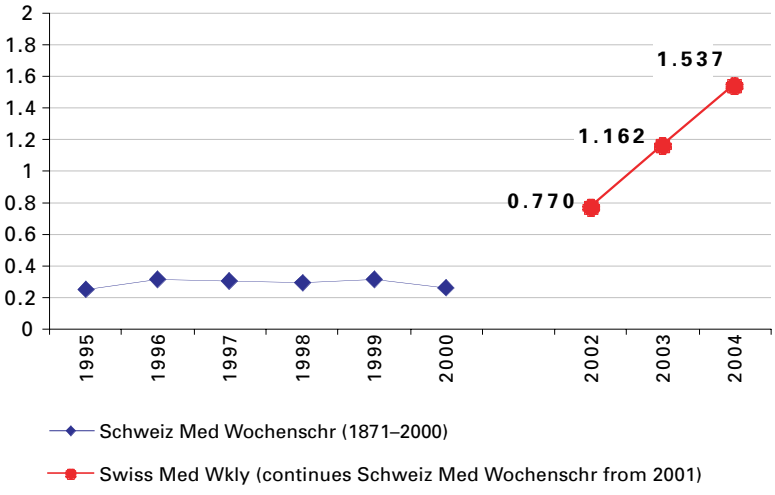

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