Dextromethorphan
An Overview of Safety Issues

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Summary
Dextromethorphan is a highly effective and widely used nonopioid antitussive drug. As it has been in use for more than 30 years, a large body of clinical experience has been used to formulate a safety profile. An anthology of adverse drug events has been analysed, drawn both from published case records and a database recording dextromethorphan-related adverse events spontaneously reported by physicians or pharmacists. The resulting safety profile indicates that adverse drug reactions are infrequent and usually not severe. The predominant symptoms are usually dose related and include neurological, cardiovascular and gastrointestinal disturbances.

Particular safety concerns arise when monoamine oxidase inhibiting (MAOI) drugs and dextromethorphan are coadministered. In addition to adverse drug reactions, the safety profile of dextromethorphan is affected by episodic and sporadic abuse. In fact, abuse appeared to be the most significant hazard identified by analysis of spontaneous adverse event reporting. No evidence could be found that the well documented pharmacokinetic polymorphism observed with dextromethorphan is correlated with any clinically significant safety risk if it is used for short term treatment. In summary, the safety profile of dextromethorphan is reassuring, particularly relating to overdose in adults and children.
Dextromethorphan is the methylated dextro-rotatory analogue of levorphanol. It acts on the cough centre in the medulla oblongata, raising the threshold for the cough reflex. The pharmacological properties of the drug have been extensively investigated as far back as 1953. Dextromethorphan is well absorbed from the gastrointestinal tract. It is metabolised in the liver (first-pass effect) and excreted in the urine either unchanged (see section 2 below), or as demethylated metabolites including dextrorphan, which itself has some cough-suppressing activity. Dextromethorphan does not inhibit ciliary function, thus providing a clinically significant advantage of the drug over many other cough suppressants. The superior efficacy of dextromethorphan in comparison with opioid antitussives has been demonstrated in several well controlled studies (Karttunen et al. 1987; Matthys et al. 1983).

In humans dextromethorphan lacks the pharmacological characteristics of opiate alkaloids. In normal individuals at therapeutic doses dextromethorphan is devoid of analgesic, euphoriant and physical dependence-producing properties (Jasinski 1979). In animals dextromethorphan is non-addictive, even in high experimental doses. Dextromethorphan became widely used in the 1950s and is now marketed in more than 60 countries under many different proprietary names on its own or in combination.

Adverse effects with dextromethorphan have a very low, but not precisely quantifiable incidence (Reynolds 1989). Considering the widespread use of dextromethorphan, there are very few reports of toxicity at recommended concentrations. Most reports of toxicity occur at high dosages as a result of misuse, ingestion with suicidal intent, or recreational use. In addition, the evaluation of toxicity is complicated by simultaneous ingestion of other substances and by the lack of objective measurements of dextromethorphan exposure.

Most of the data from clinical trials were generated in the 1950s and 1960s. The more recent trials, reviews and case reports confirm the earlier findings that adverse reactions are mild (Bickerman 1984; Matthys et al. 1983). In contrast to more conventional drug safety considerations, dextromethorphan has been the subject of abuse. These episodes have occurred sporadically over the past 30 years giving rise to self-limiting localised outbreaks characterised by symptoms of overdose among a limited segment of the population. Following such abuse episodes, cases of psychological dependence have been reported, but there does not appear to be any evidence of dependence of the morphine type.

Recently, the discovery of the polymorphic oxidation of debrisoquine caused a resurgence of interest in genetic factors affecting the individual response to drugs. In fact, dextromethorphan has been used as a prototype in the study of polymorphism in the metabolism of a wide variety of pharmacological substances (Perault et al. 1991). It has been suggested that dextromethorphan may provide a useful diagnostic tool to identify persons with deficiency in the debrisoquine-type of drug oxidation (Chen et al. 1990a). However, the recognition of dextromethorphan polymorphism also raises questions related to the safety of dextromethorphan in the minority of people who are poor metabolisers. In this respect, the dysphoric effects elicited by high doses (240mg) of dextromethorphan are probably manifested differently in poor metabolisers (Musacchio et al. 1989).

1. Spontaneous Adverse Event Reports

A relatively small number of adverse drug events (ADEs) during the past 30 years has been collected in a data base of spontaneously reported dextromethorphan-related adverse events maintained by the Drug Safety Department at Roche. ADEs are defined to include all reports affecting safety, potency, adverse reactions, clinical side effects and drug abuse problems. The drug safety data base draws upon a worldwide network of physicians and pharmacists who are actively encouraged to report upon a wide variety of prescription and over-the-counter (OTC) pharmaceutical products. A high level of cooperation is ensured by competent personnel who are assigned to evaluate the significance and severity of reports from all sources. Ad-