Lareb
Nederlands Bijwerkingen Centrum
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Neuropsychiatric side effects associated with dextromethorphan

Introduction

Dextromethorphan is an antitussive morphinan that exerts its action through an unknown non-opioid mechanism [1]. It has been approved in the Netherlands since 1974 and is available as an 'over-the-counter' product. Dextromethorphan is available as various brand names (i.e. Darolan®, Daromefan®, Romilar®, Vicks®, Rami®, Dextromethorfan-stroop Samenwerkende Apothekers®, Pectofree®, Dampo®, Tussipect® and Bussoltussin®). In the SPC it is stated that the drug may cause *excitation and confusion [2].* The only exception is the SPC of "Dampo bij droge hoest [3]" where except for somnolence, no neuropsychiatric ADRs are mentioned.
In 1998 the Netherlands Pharmacovigilance Centre together with the Inspectorate of Health published a short report on possible neuropsychiatric Adverse Drug Reactions (ADRs) associated with the use of dextromethorphan [4]. More recently the Food and Drug Administration issued a Talk Paper to notify the public about the possible abuse of dextromethorphan. Indeed, on the internet many websites exist which provide information on how to use dextromethorphan as a recreational drug. An example is "A guide describing the effects and dangers of recreational dextromethorphan use and abuse; including known deaths" [5].

Reports

Until June16 2005, the Netherlands Pharmacovigilance Centre Lareb received 43 reports on dextromethorphan. In 9 reports neuropsychiatric ADRs have been associated with the use of this drug. The mean age of the patients involved was 39.6 years (range 22-65 years). In one report (patient C) a possible overdosage has been mentioned; one patient also used alcohol.

Table 1. Reports of neuropsychiatric ADRs associated with the use of dextromethorphan

Patient, Sex, age	Dosage-form and Dosage	Concomitant medication	Suspected adverse drug reaction	Time to onset, outcome
A F, 31	dextromethorphan syrup 6 mg 6 times daily	ethinylestradiol/ gestodene beclomethason spray	excitation, anxiety	time to onset and outcome not reported
B F, 22	capsule 29.5 mg tid	ethinylestradiol/ gestodene	panic attack	9 hours, recovered
C M, 41	syrup 2,2 mg/ml Possible overdosage (3-fold)	beclomethoason spray	visual hallucinations, delusion	couple of hours, recovered
D F, 44	syrup 3 mg/ml 15 mg 4 times daily	amitryptylinum 25 mg 1dd2	speech disorder, concentration impaired, amnesia, agitation, dizziness	time to onset and outcome not reported
E F, 65	capsule 15 mg 2 times daily 1 capsule	not reported	anxiety disorder, confusion	3 days after start
F M, 29	capsule 29.5 mg 1 daily	not reported	feeling high	not reported. possible interaction with alcohol
G F, 46	syrup 2.2mg/ml 4 dd 33 mg	not reported	hallucinations, headache, vomiting	4 hours after start
H	syrup 1.5 mg/ml	not reported	paranoid reaction,	time to onset not

Patient, Sex, age	Dosage-form and Dosage	Concomitant medication	Suspected adverse drug reaction	Time to onset, outcome
M, 22	Not reported		anxiety, visual hallucination	specified. Treated with haloperidol.
I M, 56	capsule 29.5 mg 1 daily	thyroxin	hallucination, confusion	

Other sources of information

Literature
There are a few case reports in literature concerning neuropsychiatric symptoms on dextromethorphan. Manic symptoms were induced in a bipolar patient on lithium by use of a cold preparation containing dextromethorphan [6]. This 35-year-old woman had a history of major depressive episodes before experiencing mania, which had responded well to lithium therapy. When she used the medication containing dextromethorphan for an upper respiratory infection, she re-experienced many of the effects she associated with her prior mania, including insomnia, anxiety, and a 'hyped-up' feeling. Visual hallucinations occurred in a 32-year-old female on chronic fluoxetine therapy, after she used dextromethorphan cough syrup. Her hallucinations lasted 6 to 8 hours [7].

Databases
The WHO database contains 481 reports on dextromethorphan (data lock 16 June 2005). 17 Reports concern anxiety, 3 reports delusions and 37 reports hallucinations. Since dextromethorphan is an over-the-counter drug, no additional information on usage data in the Netherlands are available from the GIP-database.

Mechanism
From animal studies it is known that dextromethorphan may pass the blood-brain barrier which may explain the reported ADRs [8].
Phenotyping has found that poor metabolizers of dextromethorphan vary from approximately 1% to 10% in different ethnic groupings based on genetic polymorphism with respect to debrisoquine oxidation. For Caucasian populations in Europe the prevalence is 7.4% [9]. Especially this group may be more prone to develop these serious ADRs.

Conclusion
Dextromethorphan containing products may cause serious neuropsychiatric ADRs, among which hallucinations. Moreover, recent messages from the FDA and a search on the internet revealed that there is a potential risk for abuse of this over-the-counter product related to the occurrence of these neuropsychiatric symptoms.

References
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