The role of pharmacoepidemiological studies in the market withdrawal of carisoprodol (Somadril®) in Europe

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ABSTRACT

Carisoprodol is a centrally acting muscle relaxant that has been marketed in Europe for more than 45 years. In November 2007 the European Medicines Association recommended suspension of all carisoprodol containing products in all EU countries. During recent years, several observational studies on carisoprodol have been published by our group, which works in the field of traffic medicine and pharmacoepidemiological research in general. In this paper, we review the role pharmacoepidemiological studies on carisoprodol played in providing evidence for the risk of psychomotor impairment and traffic accidents, intoxications and abuse. These issues have been important for decisions about the regulation of carisoprodol.

Key words: pharmacoepidemiology, carisoprodol, drug abuse, impairment, intoxication

INTRODUCTION

Carisoprodol was developed in the late 1950's (1-3) and was first marketed for muscle pain, lower back pain, rheumatoid arthritis, arthrosis deformans, spondylosis, myositis and tension headache. It was introduced in the pre-benzodiazepine era as an alternative to the problematic barbiturates and barbiturate-like drugs (4). Carisoprodol was chemically based on the barbiturate-like drug meprobamate. Preclinical studies (in dogs) indicated hydroxyl-carisoprodol to be the main metabolite (5), but later clinical studies revealed that the main metabolite in man was actually meprobamate (6,7).

At that time, relatively little documentation was required to obtain market authorisation. It was not until phocomelia in the 1960's was identified as a dramatic risk associated with thalidomide exposure during pregnancy (8), that regulatory agencies worldwide set up guidelines on the documentation needed for a reasonable assessment of the benefits versus risks of new drugs. Requirements for pre-clinical, pharmacological and clinical documentation in particular have increased enormously in order for new substances to receive approval today.

After its introduction to the market, carisoprodol was tested for a series of indications. These include fibromyalgia (9,10), multiple sclerosis (11), dental pain (12) and heterogeneous groups of hospitalized patients with different musculo-skeletal disorders (13-16). The quality of these studies is questionable.

For the treatment of acute lower back pain, five different randomized controlled trials have been performed comparing carisoprodol with placebo (17-19), propoxyphene (19), butabarbital (18), diazepam (20) or cyclobenzaprine (21). Three of these studies are of high quality (18,20,21) and have been included in systematic reviews and therapeutic guidelines for the treatment of *acute lower back pain* (22-25).

Even in these early clinical experimental studies, adverse events of carisoprodol were reported. It was indicated that carisoprodol could cause dizziness (11-14,20,21,26), drowsiness (12-14,20,21,26-28), nausea (13,14), dermal complications (29), and psychomotor impairment (27). The impairing symptoms have been described as being "drunk" (30, 31). It has, however, been claimed that carisoprodol will not produce psychomotor impairing effects when taken in normal therapeutic doses (350-700 mg orally) (32-34), but has this type of effect when taken in supra-therapeutic doses (≥1150 mg) (27). However, this was not a complete picture of adverse effects.

PHARMACOEPIDEMIOLOGICAL STUDIES

Pharmacoepidemiology is the study of drug use and the effects of drugs in a large number of randomly non-selected people (35). Pharmacoepidemiology is a relatively new applied field, linking clinical pharmacology and epidemiology. Pharmacoepidemiological studies are post-marketing studies which traditionally:

1) supplement the information available from pre-marketing studies, giving a better quantification of the beneficial effects of the drug and incidence of known adverse events.
2) provide new information, such as identification of previously unknown adverse and beneficial effects, the effect of drug overdoses, the patterns of drug use (including abuse), and the economic implications of the use of the drug.

Pre-marketing studies tend to be artificial. Important subgroups of patients are typically excluded, for example, elderly people, children, pregnant women and individuals with drug abuse problems. Post-marketing studies can address this. They can also investigate how co-morbidity and co-medication modify the effects of drugs. Studies on how a drug is actually used are only feasible after it is launched. Lastly, pre-marketing studies are time-limited and often involve at the most 500-3000 subjects, which makes less common adverse reactions difficult to detect (35).

For older drugs like carisoprodol, pharmacoepidemiological research can play an important role in the post marketing monitoring of benefits and risks for three reasons. The evidence of efficacy was scant at the time of marketing and further studies are needed both on effectiveness and safety. Pharmacoepidemiological studies can, for any drug, provide new information which was impossible to obtain in even the best clinical experimental studies. Pharmacoepidemiological studies are essential for the study of certain adverse events such as psychomotor impairment, intoxications and drug abuse. Our group has published a number of studies on these topics and in this review we will describe how these studies have contributed to the process leading to the withdrawal of carisoprodol from the Norwegian market.

PSYCHOMOTOR IMPAIRMENT

The clinical experimental studies indicated that carisoprodol could cause drowsiness and psychomotor impairment. Forensic toxicologists and clinicians encountering patients who had used the drug were given an impression of heavy psychomotor impairment. Three studies on apprehended drivers shed light on this adverse effect of carisoprodol. First, a case series by Logan and co-workers indicated that carisoprodol by itself could cause traffic related impairment with blood drug concentrations within the range observed with normal therapeutic use (36,37). Second, an analysis of secular trends from our group showed that drivers using carisoprodol were stopped by the police and that the number of drivers related closely to the amount of carisoprodol sold to the population (38). Last, a study of drivers who were stopped under suspicion of driving with impairment and who were shown to be using carisoprodol, demonstrated an increasing traffic related impairment with increasing concentrations of the drug (39).

It was one issue to establish the psychomotor impairing effects of the drug and another to demonstrate that these effects had consequences in relation to traffic accidents. In a cohort study, where the Norwegian prescription database (NorPD) was coupled with the Norwegian traffic accident register and the central population registry, we showed that patients who filled a prescription for carisoprodol had almost four times higher risk of being involved in a traffic accident resulting in injury during the week following prescription (40). This study also shows the value of Norwegian registries and the benefits of being able to link these registries together for research purposes.

INTOXICATIONS

Carisoprodol can cause severe intoxication when taken in overdose. This has been illustrated by several case reports over the years (6,31,41-44). These reports, in addition to drawing our attention to the fact that carisoprodol could cause intoxication, also showed that the signs and symptoms of carisoprodol intoxication are qualitatively different from those caused by meprobamate. Whereas meprobamate intoxications cause coma or semi-comatose conditions, hypotension, flaccid muscles and absent reflexes (45-54), it was noted as early as 1959 that children became agitated after the ingestion of a single dose of carisoprodol 1200 mg (55). Other signs and symptoms of carisoprodol intoxications are coma or semi-comatose states, nystagmus, increased heart rate with normal or elevated blood pressure, seizures or cramps, increased muscle tonus and hyperreflexia or myoclonus (6,31,41-44,56). This brought our attention to the fact that carisoprodol might produce what is also known as the serotonin syndrome, which has high mortality rates and is more normally associated with the use of antidepressants (57).

Through this research it became more and more clear that carisoprodol had a relatively narrow therapeutic index. A narrow therapeutic index means that the difference between what could be considered a therapeutic intake and an intake that could cause symptoms of overdose is relatively small.

A narrow therapeutic index was further supported by other observations. Figures on emergency room visits indicated that there was a rise in the number of carisoprodol intoxications in the USA during the late 1990's (58). According to the DAWN database on emergency department drug abuse episodes for 2001, carisoprodol was the 17th most often encountered drug, with almost 1% of the mentions (N = 11,239). Counting only medicinal drugs, it ranked number 9; surpassed only by benzodiazepines, ibuprofen, and paracetamol. The use of carisoprodol in mono-intoxication suicides and suicide attempts has been confirmed in a recent publication (59).

The figures above were supported by two Norwegian studies (60,61). In these studies, there was a close

temporal relationship between the amount of carisoprodol sold in Norway and both the number of contacts made to the Poisons Information Centre and the number of forensic autopsies where carisoprodol was found. Moreover, the numbers were very high relative to other drugs, which further support the idea of a narrow therapeutic index. These result are also confirmed in a study in Texas by Forrester (62).

ABUSE

Abuse and dependence on drugs are difficult to study in controlled settings before a drug is marketed. One early experimental study, using multiple doses of carisoprodol, tried to study this topic but failed to demonstrate either pleasurable effects or withdrawal signs after regular administration (32). Several later case reports, however, described carisoprodol abuse and dependence (63-68). These case reports described drug-seeking behaviour, the use of multiple prescribers, escalating doses and clear abstinence symptoms including anxiety, tremor and insomnia after discontinuation (68-70). No studies have compared the abuse potential of carisoprodol with that of meprobamate, but several authors claim that abuse and dependence, or at least the withdrawal signs following the misuse of carisoprodol, are in fact due to carisoprodol's metabolite meprobamate (66,68,69,71).

For more systematic analysis of the abuse potential of a drug, one is often left with alternative data sources like intoxication data or data on drugged drivers. However, one study from our group using the Norwegian prescription database tried to estimate the magnitude of harmful use of carisoprodol in the whole population (72). The study identified that 2.4% of Norwegian women and 1.3% of men ≥ 18 years filled a prescription for carisoprodol at least once during 2004. The prescribing of carisoprodol was heavily skewed, with the 1% highest users of carisoprodol receiving as much as 18 percent of the total amount of the drug prescribed. According to other sources such skewness may indicate drug abuse (73,74). A further indication of non-therapeutic use was that as many as 32% of the patients received more than 15 defined daily doses (DDDs) of carisoprodol and more than 11,000 patients (15%) received 75 DDDs or more during that year. High users of carisoprodol also received high amounts of benzodiazepines and opioids. Few patients used three or more doctors for prescriptions, but carisoprodol-abusing patients more often received their prescription from high prescribing doctors. This study showed that abuse of carisoprodol was potentially a major issue. In order to allow studies of the abuse potential of a drug, a certain amount of drug use must occur in the population. The level of carisoprodol exposure in Norway and data registered in the NorPD made research on the abuse of carisoprodol feasible.

THE REGULATORY FATE OF CARISOPRODOL

Until 1995, carisoprodol was available both as a mono-substance in a tablet containing 350 mg (Somadril) and as a combination product containing carisoprodol 200 mg, paracetamol 160 mg and caffeine 32 mg (Somadril comp) in Norway. Both drugs had long been questioned among healthcare professionals, both through anecdotal reports of patients' becoming addicted and pharmacists' reporting on high prescriptions of the drug (long term treatment in high dosages) in individual patients (63,75). The benefit risk ratio for the combination drug was reviewed and found negative and this led to withdrawal initiated by the Norwegian Medicines Agency in 1996. When the combination product (containing 200 mg carisoprodol) was taken off the market, there was a compensatory increase in the sales of the pure carisoprodol product (containing 350 mg carisoprodol) (38). The withdrawal of Somadril comp was followed by the withdrawal of three other similar products the same year: Lobac (clormezanon 100 mg, paracetamol 450 mg), Trancopal (clormezanon 200 mg) and Norgesic (orphenadrin 35 mg, paracetamol 450 mg). A major reason for these withdrawals was lack of documentation for the benefits of fixed combinations (76).

The benefit risk ratio for the carisoprodol mono product was reviewed at the same time and resulted in a restriction of the indication to the treatment of acute lower back pain. The maximum recommended period of continuous use was restricted to one week, the package size restricted to 30 tablets and the product had to be prescribed according to the same guidelines as benzodiazepines and weak opioid analgesics (prescription category B).

In spite of significant restrictions for the use of carisoprodol as a mono substance, the concomitant withdrawal of several centrally acting analgesic products in fact led to the increased use of carisoprodol (77). Still there was concern among healthcare professionals about the risk of addiction (78), but only few adverse drug reactions were reported to the Norwegian Medicines Agency. A thesis by Jørgen Bramness in 2005 (79) gave a thorough review of all known data about carisoprodol up to that date, including studies published by him and his co-workers (38,39,57,80,81) These were the first studies indicating that carisoprodol was prescribed in such a way that there was strong evidence for drug abuse/addiction, (38) a high risk of intoxication (57) and a risk of impaired psychomotor functioning (38,39).

On the basis of these publications and later studies which substantiated the abuse potential of the drug (72), the increased traffic accident risk (40) and the intoxication dangers (60,61), the Norwegian Medicines Agency again started a review of the benefit risk ratio of carisoprodol. This concluded that the risk benefit balance was negative. The Agency recommended the marketing authorisation holder (MAH) to

voluntarily withdraw the product from the market. A withdrawal was agreed to by MAH and a procedure was agreed for phasing the product out of the market (82). The prescribing rules were changed moving the drug to the strictest prescribing group along with narcotics (prescribing category A) from 1st August 2007 with a total withdrawal by 1st May 2008. Healthcare professionals have responded positively to this regulatory action (83), but The Norwegian Medicines Agency have received numerous calls from patients claiming they will lose the only drug that can help them with their chronic pain conditions.

According to Art 107 of the European Union (EU) Directive 2004/83/EU a member state has to inform the EU Commission, the European Medicines Agency (EMEA) and all other member states when it considers that a marketing authorisation should be suspended, revoked or otherwise changed. The Norwegian authorities did this in April 2007 and an Art 107 referral was initiated in the EU. In November 2007 the referral was finalised and it was concluded that the benefit/risk for carisoprodol was negative. A suspension of the marketing authorisation for all carisoprodol containing products in EU countries was recommended. The timelines for the suspension is expected to be given in the awaited Commission Decision. Ultimately the future use of carisoprodol in Norway will to some extent depend on the impact of this decision. As long as the carisoprodol containing drugs have a marketing authorisation in any country, we might expect a certain degree of compassionate use of carisoprodol. Such prescriptions in Norway will be tracked using data from the NorPD. In any case, some patients may need to use alternative drugs for their conditions. These changes in pharmacotherapy in Norway will also be followed closely using the NorPD.

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