

CASE REPORT

Occupational asthma from tafenoquine in the pharmaceutical industry: implications for QSAR

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Abstract We report occupational asthma and rhinitis in a formulation pharmacist, employed in the development of tafenoquine. Tafenoquine is a new anti-malarial drug in development; the pure drug substance has an asthma hazard index of zero and previously was not known to be a respiratory sensitizing agent. The implications of this finding for the refinement of quantitative structural analysis of asthmagenic chemicals are discussed.

Key words Asthma hazard index; respiratory sensitizer; tafenoquine.

Introduction

Tafenoquine is a new anti-malarial drug, which previously was not known to be a respiratory sensitizing agent. The asthmagenic potential of low-molecular-weight organic agents can be predicted using the quantitative structure-activity relationship (QSAR) model [1], but the pure drug substance of tafenoquine has an asthma hazard index (HI) of zero, suggesting that it has no respiratory sensitizing potential.

Case report

A 38-year-old pharmacist employed in the UK pharmaceutical industry had, for 2 years, been involved in the development of a drug product formulation of a novel anti-malarial compound (tafenoquine). He had a history of childhood asthma, which had not troubled him since early teenage, and of hay fever; he had never been a smoker. He was referred following two incidents of severe rhinitis, each following airborne exposure to powdered tafenoquine during tablet manufacture, and each accompanied by wheeze and breathlessness. On each occasion too, his rhinitis lasted for several days. The first episode occurred at a contract manufacturing plant overseas, the second following pilot plant work in the UK.

At his first consultation, he had been restricted from working with the compound for several months

following the second incident. He had a forced expiratory volume in one second (FEV₁) of 4.2 l (100% predicted) and a forced vital capacity of 5.6 l (114%), with only minimal improvement (<5%) after inhalation of salbutamol. His histamine PC₂₀ was 2.5 mg/ml indicative of mild non-specific bronchial hyper-reactivity. He had immediate skin prick test reactions to extracts of grass pollen and cat fur. Specific skin prick testing was not attempted; an in-house assay for serum-specific IgE antibodies to tafenoquine was negative. His chest radiograph was normal. An examination of his nose revealed no polyps.

We looked for supporting evidence that tafenoquine could be a respiratory sensitizer using a QSAR model that is freely available on the University of Manchester website [1]; tafenoquine has a HI of zero.

We arranged single-blind inhalation tests, on separate days using a dust tipping method in a sealed chamber. Fifteen minutes exposure to a control dust (lactose) provoked no symptoms and no changes in his FEV₁ (Figure 1). Exposure for the same duration to 1% tafenoquine in 250 mg of lactose provoked a 19% fall in FEV₁ 10 min after challenge and a greater fall (maximum 32%) at 8 h; this later reaction persisted for 24 h (Figure 1). The following morning his FEV₁ was 2.8 l. These changes in lung function were accompanied by a very unpleasant rhinitis with both a blocked nose and rhinorrhoea, which persisted for several days. We did not feel that any

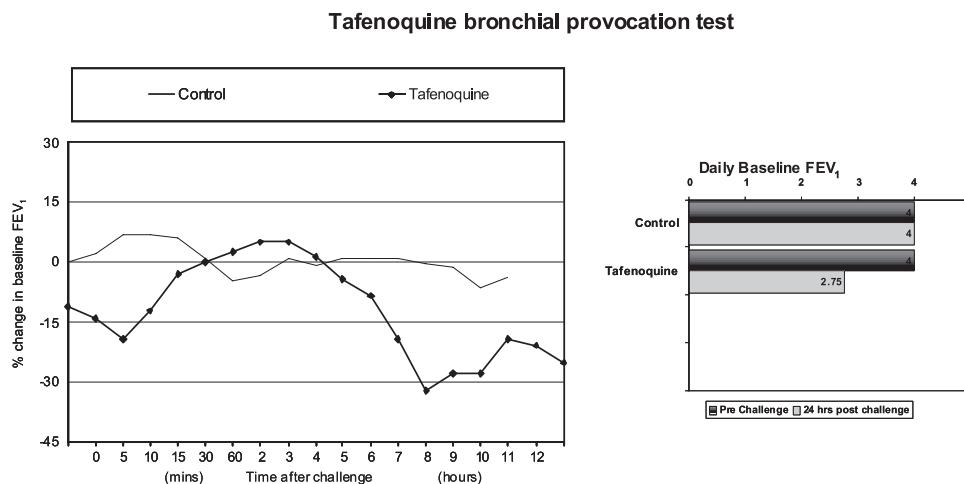


Figure 1. Results from specific inhalation challenge test with lactose (control) and tafenoquine (active).

repeat challenge with the active pharmaceutical ingredient (API) was justified.

Discussion

Tafenoquine is a novel 8-aminoquinoline drug currently under development as a potential treatment for the radical cure (relapse prevention) of *Plasmodium vivax* malaria to be co-administered as a single dose with standard doses of another anti-malarial agent [2]. Among its potential benefits is its activity in the liver stage of vivax malaria and its long half-life, which may support single-dose treatment [3]. The API is known to be a skin sensitizer [4]. Our findings show evidence, in a first case report, that respiratory sensitization is a potential hazard during tafenoquine manufacture and has led to the material safety data sheet being amended. We have no evidence to suggest that it may be similarly hazardous by ingestion.

The QSAR model that is available on the University of Manchester website [1] has been validated using an arbitrary cut-point HI of 0.5, such that compounds with HI > 0.5 are considered likely to be asthmagenic, whereas those with an index ≤ 0.5 are unlikely to have asthmagenic potential. External validations have demonstrated that the QSAR model is able to distinguish asthmagenic from non-asthmagenic compounds with sensitivities of 79–86% and specificities of 93–99% [5,6]. Tafenoquine (Figure 2) appears to be an example of a ‘false negative’ as its HI is zero despite the convincing clinical evidence described here for its respiratory sensitizing potential. Such false negatives are relatively rare but provide an opportunity for improving the QSAR model by their inclusion in learning data sets to generate further models that are based on a wider range of chemical structures shown to be asthmagenic.

It is interesting, however, to consider mechanistically why the existing QSAR model does not predict

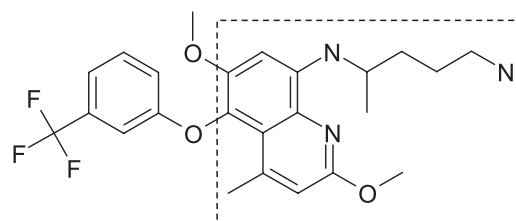


Figure 2. Molecular structure of tafenoquine (CAS No. 106635-80-7). The portion enclosed by dashed lines is the likely substructural fragment responsible for its asthmagenicity.

tafenoquine to be a respiratory sensitizer. The likeliest moiety of the tafenoquine molecule responsible for initiating asthmagenesis by binding to human macromolecules is that containing the three nitrogen atoms [7]. When this moiety (contained within rectangular enclosure in Figure 2) was considered as a hypothetical separate fragment, the HI increased to 0.89. Primaquine is an already licensed anti-malarial drug whose structure is similar to the boxed moiety in Figure 2 and it has HI value of 0.64. This would be consistent with primaquine having respiratory sensitizing potential, but no cases of asthma caused by inhalation of primaquine have been reported.

Certain substructural fragments, such as the fluorine atoms and ether groups external to the rectangular enclosure in Figure 2, were found by Jarvis *et al.* [5] to be more frequent in control than asthmagenic compounds used in the model development. They, therefore, have had a strong negative influence in the logistic regression equation that generated the asthma HI values. A continual iteration of the QSAR model, by inclusion of newly identified asthmagenic compounds such as tafenoquine in larger learning data sets, is likely to improve its predictivity. This example also illustrates why a predictive algorithm that also utilizes expert mechanistic chemistry or qualitative structure–activity relationship approaches, whilst not validated for use alone, could

help to complement the high sensitivity and specificity of the extant QSAR [8].

Key points

- Tafenoquine (active pharmaceutical ingredient) can be a respiratory sensitizer by inhalation.
- There is no evidence to suggest any hazard by ingestion.
- Analysis of the chemical structure of newly identified asthmagens such as tafenoquine offers opportunities to refine predictive models.

Conflicts of interest

A.J. is employed and holds stock with GlaxoSmithKline, the makers of tafenoquine.

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