Benzbromarone: availability for general prescribing in New Zealand (a response to letters by Dr Lance Gravatt on benzbromarone)

We read with interest the letters from Dr Lance Gravatt concerning the hazards of prescribing benzbromarone, a potent uricosuric agent indicated for the prevention and treatment of gout.¹,²

The drug, although not registered in New Zealand by Medsafe, has been made available via PHARMAC since July 2013. The arrangements for access are clear: failure to tolerate allopurinol or failure to reach a target plasma urate concentration of 0.36 mmol/L despite dose escalation of allopurinol. Further, regular liver function tests are recommended.

Dr Gravatt notes two potential hazards:

1. Bleeding risk in patients taking warfarin because of benzbromarone inhibition of warfarin metabolism by hepatic cytochrome enzymes, and
2. Hepatotoxicity, recently the subject of a warning from the Japanese Medicines Regulatory Agency (PMDA).³

Our own analysis published in 2008 concerning the availability of benbromarone⁴ noted that the grounds for withdrawal of the drug from the European market by the patent holder Sanofi in 2003, because of hepatotoxicity, was questionable. This opinion was based on the paucity of cases compared to the heavy usage rates, potential for other mechanisms to be involved in the cases available to us for scrutiny and economic considerations.

We went on to recommend access to and use of the drug if alternative therapies, mainly allopurinol, were not tolerated or were unsuccessful in achieving a satisfactory reduction of plasma urate concentrations despite dosage escalation. We also noted that the drug needed to be used carefully in full knowledge of the risks and need for adequate monitoring.

Dr Gravatt notes that, since our analysis, another hypouricaemic drug (that he has a pecuniary interest in) has been registered widely. Febuxostat is a xanthine oxidase inhibitor that is effective and well tolerated although there has been a suggestion of cardiovascular toxicity.⁵,⁶ It is not retained in renal impairment and, again unlike allopurinol, Stevens Johnson syndrome has not emerged as a significant hazard. Why then has PHARMAC made benzbromarone available but not febuxostat?

New Zealand researchers Dalbeth, Stamp, Gow, Barclay and O'Donnell have lead the World in the ‘treat to target’ plasma urate approach to dosing with allopurinol.⁶,⁷ It is apparent that we have been under-dosing many patients with allopurinol and are loath to increase the dose above 300 mg/day for fear of serious hypersensitivity reactions. By increasing the dose slowly and promoting adherence long-term, it is possible to accommodate a much greater proportion of gout sufferers and bring their plasma urate concentrations down to safe levels—e.g. less than 0.36 mmol/L.
Allopurinol, probenecid and benzbromarone all work and in most markets cost a lot less than febuxostat. Once a drug is available under subsidy it tends to get used much more widely than needed and unnecessary costs to the taxpayer follow. Presumably cost-effectiveness has had something to do with PHARMAC’s action.

We second Dr Gravatt’s suggestions that good information about the hazards with benzbromarone be promulgated widely, and that, in the first instance, prescribing be restricted to rheumatologists when alternative drugs, notably allopurinol, cannot be used. We would be surprised if most initial prescribing of benzbromarone was not undertaken by rheumatologists.

Enhanced monitoring of INR in those on warfarin, and dose adjustment if needed, is important. Also, hepatic function review regularly, especially in the first 6 months, as recommended by PHARMAC, with patients warned of relevant symptoms is mandatory. However, it would not be expected that there would be a large proportion of gout patients would ever need to be prescribed benzbromarone.

Finally, until the price of febuxostat renders this option ‘cost-effective’ for a national buyer like PHARMAC or PBS in Australia, the odds of seeing it on subsidised list seem poor.

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