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LETTERS

LONG ACTING 2 AGONISTS IN ADULT ASTHMA

Use long acting β2 agonists only when asthma cannot be controlled otherwise

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When reviewing the value of long acting β2 agonists in the treatment of asthma,[1] Currie and colleagues did not properly report the results of one of the major studies, the Salmeterol Multi-centre Asthma Research Trial (SMART).[2]

When salmeterol was approved in the US in 1994, the Food and Drug Administration asked the manufacturer to run a large scale placebo controlled safety trial owing to accumulating concerns about the safety of long acting β2 agonists, particularly salmeterol.[3] In contrast to Currie and colleagues, SMART showed significant differences in major endpoints in favour of placebo.[3] According to the SMART protocol, an interim analysis was to be performed after 30 000 patients were recruited. The protocol called for SMART to be terminated if evidence was found that salmeterol led to an increase in the primary endpoint or asthma related death. Termination criteria were defined as a relative risk of 1.4 for the primary endpoint and of 3.0 for asthma related deaths.[3] SMART was prematurely terminated in January 2003, and 26 355 patients were included in the final analysis.

The endpoints of respiratory related deaths (relative risk 2.16), combined asthma related death or life threatening experiences (1.70), and asthma related deaths (4.37) occurred significantly ($P<0.05$) more often in the salmeterol group. There is no doubt that the prespecified early termination criteria were reached. It would have been unethical to recruit additional patients to confirm the excess salmeterol associated mortality for the primary endpoint with statistical significance.[3] The FDA even prepared a video to publicise these results. The number needed to harm for death from any cause was 1316 for patients treated for 28 weeks with salmeterol. The excessive risks seen in African-Americans, which Currie and colleagues emphasised, are the result of a subgroup analysis not prespecified in the trial protocol.

Finally, convincing evidence that concurrent treatment with inhaled corticosteroids nullifies risks related to long acting β2 agonists is missing.[4] Thus, the use of these agents for asthma should be restricted to patients whose disease cannot be controlled otherwise.

Competing interests: None declared.

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2 Hasford J, Virchow JC. Excess mortality in patients with asthma on long-acting beta2-agonists. *Eur Respir J* 2006;28:900-2.
3 Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM; SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;129:15-26.
4 Food and Drug Administration. Joint Advisory Committee. Background on safety issues with long-acting beta agonists for asthma. 2008. www.fda.gov/ohrms/dockets/ac/08/slides/2008-4398s1-03-Mosholder.pdf.

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