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Recurrent anaphylaxis to synthetic folic acid

Food fortification with synthetic folic acid (pteroylmonoglutamic acid) remains a source of debate in terms of benefit versus issues of safety and consumer choice.¹ Several countries have adopted mandatory folic acid fortification. A decision to proceed in Australasia was made in June, 2007.

We report the case of a woman who had three episodes of type I hypersensitivity, including anaphylaxis, after synthetic folic acid exposure. Her first episode occurred within minutes of taking a 5 mg folic acid tablet. She developed an itchy throat, nausea, generalised rash, diarrhoea, and lightheadedness; she was treated with antihistamines. The second episode followed consumption of 800 mL lime-flavoured water fortified with 20 µg/100 mL folic acid. Within minutes of finishing the drink she developed an itchy throat, generalised pruritus, and nausea. She was treated with adrenaline and antihistamines. A further episode occurred within minutes of drinking 150 mL of a beverage containing feijoa (a fruit of the Myrtaceae family) and supplements including 53.5 µg/100 mL folic acid. She developed generalised rash, vomiting, and lightheadedness. Adrenaline was given en route to hospital, with good response.

Intradermal testing with folic acid 0.05 µg/mL solution containing folic acid, bicarbonate, and water was positive (9 mm wheal, 35 mm flare). A control patient was negative. Skin-prick tests to other food and beverage products were negative. A graded, blinded challenge to the folic acid solution led to widespread urticaria at a dose of 160 µg.

Before her first episode she had taken a multivitamin B supplement and recalled recurrent episodes of urticaria, and presumably sensitisation to folic acid occurred at this time. She seems to tolerate dietary folates (pteroylpolylglutamates).

Hypersensitivity to synthetic folic acid has been rarely described.²⁻⁴ One

report documents sensitivity to synthetic folic acid in medication, as a food supplement, and possibly to dietary folate.² In a further case of anaphylaxis after folic acid exposure in multivitamin preparations, development of IgE antibody to folic acid was shown by in-vivo and in-vitro testing.³ In IgE-mediated reactions, folic acid, with a molecular weight of only 441 D, probably acts as a hapten by conjugation with self-proteins.³

Folic acid fortification must be accompanied by clear food labelling to enable those who develop allergy to avoid life-threatening reactions. Folic acid allergy should be considered in the differential diagnosis of idiopathic anaphylaxis and suspected cereal allergy where skin-prick or RAST testing to standard grains is inconclusive.

We declare that we have no conflict of interest.

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DFID's health strategy

In your June 16 Editorial (p 1973),¹ you praise the new health strategy of the UK's Department for International Development (DFID),² and its "rather unusual, but much needed, donor practice of budget support". However, this strategy fails to address one crucial limitation: the International Monetary Fund (IMF) policies which

dictate that a significant proportion of budget support remains unabsorbed or unspent.

A report of the Independent Evaluation Office of the IMF reveals that, since 1999, around 37% of additional foreign assistance to countries in sub-Saharan Africa under IMF programmes was explicitly designed to increase international reserves.³ Of the 63% designed to be absorbed, only 28% was supposed to be spent; the other 72% was programmed to increase public savings. In all, the IMF programmed 28% of 63% of additional foreign assistance—a ridiculous 17.64%—to be both absorbed and spent. This "IMF tax", as one observer has described it,⁴ reduces the real amount budget support that can actually be spent by 82.36%.

At a seminar in London on April 2, 2007, the lead author of the independent evaluation recommended that the IMF should be transparent about this policy of limiting countries' ability to spend foreign assistance. However, the Board and management of the IMF rejected the recommendation, on the grounds that secrecy gave them more flexibility.⁵

DFID's new health strategy paper cites the integration of grants from the Global Fund to fight AIDS, Tuberculosis and Malaria to Mozambique into the health Sector-Wide Approach (SWAp) as an example of the "potential of country-led aid instruments to achieve aid harmonization and alignment".² However, it could also mean that the Global Fund grants are now subjected to the IMF tax, severely limiting the amount that can actually go towards improving health care. Since the IMF prefers to keep this "tax" secret, we might never find out.

DFID, the IMF, and the Global Fund should state clearly how they will guarantee that budget support to the health sector will be entirely absorbed and spent, rather than "taxed" by the IMF. Without a clear position on this issue, the amount of foreign assistance provided in the form of

budget support must be examined with extreme caution.

We declare that we have no conflict of interest.

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- 4 Hanlon J. IMF makes major concessions on wages & aid. <http://www.open.ac.uk/technology/mozambique/pics/d55391.doc> (accessed June 29, 2007).
- 5 Hanlon J. IMF does cap aid, says independent evaluation. <http://www.open.ac.uk/technology/mozambique/pics/d75975.doc> (accessed June 29, 2007).

We join you in congratulating the UK government's Department for International Development (DFID) for its new health strategy¹ and recommend that readers peruse DFID's second progress report, *Reducing maternal deaths: evidence and action*.² The report's many examples show how to approach health-system strengthening by promoting reproductive health. For example, DFID has committed £252 million to reducing geographic and social disparities in access to reproductive and child health services in India by building new health facilities and expanding core medical training, not just by funding vertical family planning and child health services. This comprehensive approach has increased the proportion of institutional deliveries to 19% in one Indian state over a 7-year period, and laid a strong foundation for progress towards reducing 136 000 maternal deaths annually.² The benefits for women, families, and communities will be immeasurable.

We, like you, urge the UK government to use such evidence to hold

other large development agencies, in particular the World Bank and WHO, accountable for their commitments to reproductive health.

I declare that I have no conflict of interest.

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Misleading confidence intervals

In their randomised trial of a combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk, Francis Chan and colleagues (May 12, p 1621)¹ use the Kaplan-Meier method to estimate the probability of recurrent bleeding at 13 months. In the intervention group, no events were observed. Chan and colleagues give the estimated probability of a bleed as 0 (95% CI 0 to 0). This CI implies that there is no error in the estimate and that, in the entire population of patients that this sample represents, no bleed can ever occur within 13 months. We cannot draw this conclusion and the CI must be wrong. What Chan and colleagues seem to have done is to use a large sample method for calculation of the CI for a sample which is far too small in that no events have been observed.

Since 135 of the 137 patients were observed for 13 months, it is easy to calculate a CI by the exact binomial method, which will be roughly correct, just using the data in the published paper. If we observe zero events in 135 patients, the exact 95% CI is 0 to 0.027. The data are thus consistent with a probability of a bleed of as large as 0.027 (2.7%).

I declare that I have no conflict of interest.

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- 1 Chan FKL, Wong VWS, Suen BY, et al. Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. *Lancet* 2007; **369**: 1621–26.

Authors' reply

We thank Martin Bland for providing a more accurate method of estimating the 95% CI when no events have been observed. We have now recalculated the probability of recurrent bleeding using the exact binomial method, and the corrected 95% CIs in the combined-treatment group are shown in the table. The between-group differences remain significant and the conclusions of the paper are unchanged.

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	Probability of recurrent bleeding (95% CI) p		
	Combined-treatment group	Control group	
All patients	0% (0.0–2.6)	8.9% (4.1–13.7)	0.0004
Patients who did not take concomitant aspirin	0% (0.0–3.1)	7.1% (2.4–11.8)	0.004
Patients who took concomitant aspirin	0% (0.1–14.8)	19.0% (2.2–35.8)	0.03
Per-protocol analysis	0% (0.0–3.4)	6.0% (1.4–10.6)	0.01

Table: Exact binomial estimates of the likelihood of recurrent ulcer bleeding at 13 months