Correspondence

Adverse Drug Reaction (ADR)

This is in connection with the query raised on Adverse Drug Reaction (ADR) to Cefipime and the reply(1).

It is often difficult to ascribe 'cause and effect' in case of ADR, but it should be objectively assessed and presented based on an acceptable 'Probability Scale'. The 'Naranjo ADR Probability Scale' is an internationally accepted one, by which ADR can be classified into highly probable, probable or doubtful(2). The scale is summarized in *Table I*. It is desirable to use an objective scale and document and report ADR in a systematic way for future reference.

TABLE I–*Naranjo ADR Probability Scale–Items and Score*

1. Are there previous conclusive reports on this reaction?
   Yes (+1) No (0) Don't know (0)
2. Did the adverse event appear after the suspected drug was administered?
   Yes (+2) No (–1) Don't know (0)
3. Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered?
   Yes (+1) No (0) Don't know (0)
4. Did the adverse reaction reappear when the drug was re-administered?
   Yes (+2) No (–1) Don't know (0)
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?
   Yes (–1) No (+2) Don't know (0)
6. Did the reaction reappear when a placebo was given?
   Yes (-1) No (+1) Don't know (0)
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?
   Yes (+1) No (0) Don't know (0)
8. Was the reaction more severe when the dose increased, or less severe when dose was decreased?
   Yes (+1) No (0) Don't know (0)
9. Did the patient have a similar reaction to the same or similar drug in any previous exposure?
   Yes (+1) No (0) Don't know (0)
10. Was the adverse event confirmed by any objective evidence?
    Yes (+1) No (0) Don't know (0)

Interpretation; >9 = highly probable; >5 - 8 = probable; > 1 - 4 = possible; ≤ 0 = doubtful

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Reply

Dr. Elizabeth has raised a valid issue regarding criteria for assessing ADRs. The widespread use of the Naranjo ADR Probability Scale (NADRPS) by journals assessing manuscripts submitted for publication as case reports, suggest that although no perfect solution exists for clinicians seeking to assess the likelihood of ADRs, this scale does provide a somewhat structured basis for assessment in a standardized and relatively reproducible format. However, several of the questions in NADRPS are difficult to apply. In some situations the scale requires modification to improve reliability, validity, and clinical usefulness(1). And more often than not, using NADRPS, we are only able to confirm that the cause and effect is either 'possible' or 'probable'(2). Another drawback of the scale is that even if none of the criteria are met, the cause and effect is categorised as 'doubtful' making it difficult to categorically rule out the possibility of ADR in any given case. But, because its inter-rater reproducibility is good, IP also would use this scale while reviewing articles related to ADRs.

Studies employing a computerized monitoring system to analyse laboratory data using the NADRPS or other suitably modified criteria have found that the detection rate of ADRs may almost be

doubled(3). Automatic generation of laboratory signals when an ADR is developing helps in early identification, reduction of morbidity, hospital stay, and treatment costs. The staff in the process get tuned to suspecting an ADR.

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Bone Mineral Density and Thalassemia Major and Intermedia

We read with keen interest Karimi, *et al.* article on bone mineral density in beta thalassemia. Dual energy *X*-ray absorptiometry (DEXA) provides the measurement of the total amount of bone mineral content (BMC; g) contained within the scanned skeletal region and the two-dimensional projected bone area (BA; cm^2). DEXA does not measure the bone thickness and therefore the volume (cm^3) that is required for estimation of volumetric bone mineral density (vBMD; g/cm^3). The ratio of BMC to BA allows estimation of the areal BMD (aBMD; g/cm^2), which is a function of bone size and its vBMD. Therefore, in a child with a chronic disease, a low aBMD might be due:

(*a*) the adverse effect of the disease on his/her growth and pubertal development, resulting in smaller bones;

(*b*) impaired mineralization; or

(*c*) both these factors.

These issues are particularly relevant in patients with beta thalassemia major in whom impaired growth and hypogonadotrophic hypogonadism are well known secondary complications(2). We, therefore, were surprised that data on height, weight and Tanner stages of pubertal development for thalassemic subjects and controls were not provided by the authors. Furthermore, the authors could have compared the bone mineral apparent density (BMAD; g/cm^3) of the lumbar spine and the femoral neck, by dividing BMC by the three-dimensional bone volume derived from its two-dimensional projected BA, in their Thalassemic subjects and controls(3). They could have also compared the size adjusted BMC in the two groups. This is easily done using a regression or a multivariate statistical model to adjust the BMC for projected BA, height, weight and Tanner stages of sexual development(4).

Such approaches would have reduced the influence of any changes in bone size due to Thalassemia and secondary endocrine problems on DEXA measured bone variables. Without such adjustments, the authors' conclusion that low BMC and aBMD in their Thalassemic subjects was due to impaired mineralization is, in our opinion, less secure.

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