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Journal of Chromatography B, 853 (2007) 369–370
JOURNAL OF CHROMATOGRAPHY B
www.elsevier.com/locate/chromb

Discussion

Comment on "Determination of treosulfan in plasma and urine by HPLC with refractometric detection; pharmacokinetic studies in children undergoing myeloablative treatment prior to haematopoietic stem cell transplantation" by F.K. Glowka et al. [J. Chromatogr. B 850 (2007) 569–574]

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Received 15 February 2007; accepted 25 February 2007
Available online 24 March 2007

Dear Sir,

We read the work of Glowka et al. entitled "Determination of treosulfan in plasma and urine by HPLC with refractometric detection; pharmacokinetic studies in children undergoing myeloablative treatment prior to haematopoietic stem cell transplantation" with great interest. The work was recently published in J. Chromatogr. B (2006), doi:10.1016/j.jchromb.2006.12.020.

While the analytical part of the work is very interesting and useful, we completely disagree with the last sentence of the conclusion: "Pharmacokinetics of treosulfan in biological fluids of children after infusion of the drug demonstrates a similar pattern as in adults".

This statement is not supported by the data presented for the following reasons:

(1) The number of five children investigated does not allow drawing this conclusion even with the extreme high numbers of blood samples drawn from each patient.
(2) The applied methodology is not suitable for the question raised in the paper. Further, in Section 2.8, the method applied for pharmacokinetic analysis is not adequately described. If a two-compartment model was used to describe the data, it is not suitable to use the trapezoidal rule with extrapolation to infinity for AUC calculation. Thus, this section does not allow understanding how the analysis was done.
(3) In Fig. 4, the mean values at each time point are shown summarising the data from all patients and plotted versus time. Although this so-called naïve two-stage approach is still used especially in preclinical research, it is generally accepted that summarising data from several individuals in this way provides misleading results [1]. This can be seen from the fact that the mean 1.5 h concentration is lower than the 1 h-concentration, which is impossible with a 2 h infusion. Furthermore, for some data points like the 4 h value the difference mean−standard deviation is lower than zero indicating that the data are not normally distributed. Pharmacokinetic data are mostly log-normally distributed [2] and cannot adequately summarised using mean and S.D.
(4) It is not acceptable to summarise dose-dependent pharmacokinetic parameters like AUC, C_{max} or plasma concentration data from patients receiving different dosages.
(5) The data presented in Table 5 do not support the conclusion of "similar pattern as in adults". From the AUC of 1260 ± 949 μg/ml with this extreme high variability, no clear conclusions can be drawn.

We think that these points raised are not only of scientific value. More importantly, clinicians may draw false conclusions from the findings stated in the work of Glowka et al. itself or others may cite the work in other publications in a way stating

DOI of original article:10.1016/j.jchromb.2006.12.020.
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1570-0232/$ – see front matter
doi:10.1016/j.jchromb.2007.02.060

that there are no differences in the pharmacokinetics of treosulfan between adults and children. This may even cause a risk for patient safety. In general, in such a bio-analytical publication, it may be more appropriate to focus on the analytical results and demonstrate the applicability by showing the analysis of real samples without focusing too much on the pharmacokinetics.

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