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Alkylating activity in serum, urine, and CSF following high-dose ifosfamide in children – a comment

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1. The NBP method used here detects all alkylating metabolites that are present, that is, metabolites that may widely differ in their pharmacokinetic profile and biologic effects. In other words, the carcinotoxicity and general toxicity of the various metabolites, which cannot be separated by this method, varies considerably. The interpretive value of the results is therefore limited. Still, it should be stressed that the separate detection of, in part, highly unstable alkylating metabolites, some of which are present in very low concentrations, is generally considered very difficult.

2. Nearly all alkylating metabolites of ifosfamide have very short half-lives (< 30 min). The pharmacokinetic properties and plasma half-lives of the alkylating metabolites occurring after an ifosfamide dose, therefore, depend almost solely on their rate of formation, that is, the rate of parent compound activation. Given the decreased ifosfamide half-life after repeated administration of the drug [3, 6, 7], it comes as no surprise that the half-lives of the alkylating metabolites are also reduced. In keeping with the hypothesis of Ninane et al., this phenomenon appears to result from self-induction of enzymatic ifosfamide activation. It should be pointed out in this context that similar findings were obtained in recent years by various workers [1, 5] and by us [4, 7] for the ifosfamide analogue, cyclophosphamide. Furthermore, cytostatic drugs of the oxazaphosphorine type are known to show substantial intra- and interindividual variability in their biotransformation. Given the narrow therapeutic range of all cytostatic agents, this large variability no doubt is a problem.

3. As a result of the rapid biotransformation and shorter half-lives, the alkylating metabolites frequently reach higher initial plasma levels, which then fall more rapidly. Our studies on cyclophosphamide indicate that the concentration-time product ($C \times t$, area under the blood-level curve) is equal to or even greater than the AUC obtained under regular half-life conditions. Adequate therapeutic levels in poorly accessible compartments such as the cerebrospinal fluid certainly require high peak levels. However, the optimal duration of ifosfamide therapy and the question of whether to use bolus injections or continuous infusions would appear to depend more on the proliferation kinetics of the various tumors and, therefore, should be determined in therapeutic trials that may be complemented by cytokinetic data.

4. We developed more concrete ideas regarding the neurotoxicity of the drug. There is much evidence to suggest that chloroacetaldehyde is the metabolite responsible for the neurotoxicity of ifosfamide. In 1976, Norpoth [2] pointed out the large interindividual variability in the extent of side-chain oxidation and the formation of chloroacetaldehyde. It is conceivable that renal failure may exacerbate the CNS toxicity of chloroacetaldehyde.

References

1. Graham MI, Shaw IC, Souhamit RL, Sidan B, Harper PG, Melean AEM (1983) Decreased plasma half-life of cyclophosphamide during repeated high dose administration. Cancer Chemother Pharmacol 10: 192–193
2. Norpoth K (1976) Studies on the metabolism of isophosphamide (NSC-109724) in man. Cancer Treat Rep 60: 437–443
3. Piazza E, Catteneo MT, Varini M (1984) Pharmacokinetic studies in lung cancer patients. Cancer 54: 1187–1192
4. Schuler U, Ehninger G, Wagner T (1987) Repeated high dose cyclophosphamide administration in bone marrow transplantation – exposure to activated metabolites. Cancer Chemother Pharmacol 20: 248–252
5. Sladek NE, Priest J, Doeden D, Mirocha CJ, Pathre S, Kririt W (1980) Plasma half-life and urinary excretion of cyclophosphamide in children. Cancer Treat Rep 64: 1061–1066
6. Wagner T, Ehninger G (1986) Influence of repeated high dose treatment on the metabolism of oxazaphosphorine cytostatics. 14th International Cancer Congress, Budapest, Aug 21–27, Abstract, vol 1. Karger, Basel Munich, p 216
7. Wagner T, Ehninger G (1987) Self-induction of cyclophosphamide and ifosfamide metabolism by repeated high dose treatment. In: Brade WP, Nagel GA, Seeber 5 (eds). Ifosfamide in tumor therapy. S. Karger, Basel Munich, pp 69–75 (Contributions to Oncology, vol 26)