Cancer Chemother Pharmacol (1985) 15: 183–184

Cancer Chemotherapy and Pharmacology

Letter to the editor

Concerning the paper

Clinical pharmacology of high-dose cisplatin by Corden et al.

Sir,

Recently, Corden et al. reported the plasma kinetics of total and unbound platinum in patients receiving high dose Platinol® (40 mg/m^2 daily for five doses) therapy [1]. They obtained blood samples at 0, 15, 30, 45, 60, and 90 min after the end of a 30 min infusion on days one and five. In addition, pretreatment samples were taken daily and the results from a typical patient were reported in Fig. 1. These authors suggest that the unbound plasma platinum has a short terminal half-life of 19–31 min. However, in their calculations of the half-life of elimination they neglected to take into account the pretreatment levels of unbound platinum on days 3, 4, and 5.

By our calculations using the available data presented by Corden et al., we have determined that the disappearance of unbound platinum follows a biexponential kinetic pattern. Clearly, a short half-life of elimination of unbound platinum is seen immediately after the cessation of the Platinol® infusion. However, the accumulation of pretreatment unbound plasma platinum suggests that a prolonged second half-life of alimination is present. Without data between the 90 min and the pretreatment platinum levels, the assessment of the actual terminal half-life of elimination for the second phase is difficult. However, we predict based on the available pretreatment unbound platinum levels, a terminal elimination phase of greater than 24 h.

In conclusion, Corden et al. reported interesting results on the kinetics of total and unbound platinum in plasma. However, these authors failed to completely analyze the collected data. Upon our review of their data, a prolonged half-life of elimination for unbound plasma platinum was greater than 24 h and followed a biexponential kinetic pattern as opposed to single exponential kinetics. Further research examining the prolonged elimination of unbound platinum is warranted.

Reference

1. Corden BJ, Fine RL, Ozols RF, Collins JM (1985) Clinical pharmacology of high-dose cisplatin. Cancer Chemother Pharmacol 14: 38–41

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Answer

Sir,

A closer examination of the analytical methods involved in cisplatin measurement should help to clarify the issues raised by DeGregorio et al. [1]. In our clinical study [2], plasma samples were ultrafiltered and then total platinum content in the ultrafiltrate was measured by flameless atomic absorption spectroscopy (FAAS). The concentration of ultrafiltrable platinum present in plasma 90 min after cessation of a 30-min infusion of 40 mg/sq.m cisplatin and prior to the start of the next infusion is near the limits of detection with current instrumentation. More importantly, as we pointed out in our publication, FAAS does not distinguish among the species present in the ultrafiltrate.

Several groups have compared plasma levels of total platinum, ultrafilterable platinum, and intact cisplatin, as measured by HPLC or chemical reaction techniques [3, 4]. In all cases, the disappearance curves for intact cisplatin and ultrafilterable platinum are essentially identical for at least 90 minutes, while the curve for total platinum displays markedly slower elimination. At some point, the curves for intact cisplatin and ultrafilterable platinum also diverge. However, the point of divergence is longer than the time scale (90 min) of our study. For example, Sternson et al. [3] show convergence out to 2 h. However, at 6 h filterable platinum is still measurable but intact cisplatin is no longer detectable. Thus, we disagree with the interpretation of DeGregorio et al regarding our ultrafilterable platinum results and think that it would be incorrect to assume that there is a prolonged elimination phase of the order of 24 h.

There have been many false impressions regarding the clinical pharmacology of cisplatin due to a failure to use methodology which was specific for the chemical of inter-

est. Early studies based on measurement of total circulating platinum levels in plasma generated the impression that the half-life of cisplatin could be several weeks. We certainly don't want to add to the confusion by having our 24 hour plasma samples misinterpreted. If we had used a more specific method, we are confident that this confusion would not have arisen. However, we remain convinced that the short-term (< 2 h) plasma kinetics of cisplatin can be well-described by the very straightforward procedure of ultrafiltration.

References

1. DeGregorio MW, Wilbur JR, Crowley TJ, Deisseroth AB (1985) Letter to the editor, Cancer Chemotherapy and Pharmacology
2. Corden BJ, Fine RL, Ozols RF, Collins JM (1985) Clinical Pharmacology of high-dose cisplatin. Cancer Chemother Pharmacol 14: 38–41
3. Sternson LA, Repta AJ, Shih H, Himmelstein KJ, Patton TF (1984) Disposition of cisplatin vs total platinum in animals and man. In: Platinum Coordination Complexes in Cancer Chemotherapy (Hacker MP, Douple EB, Krakoff IH, eds) Martinus Nijhoff, Boston
4. Andrews PA, Wung WE, Howell SB (1984) A high-performance liquid chromatographic assay with improved selectivity for cisplatin and active platinum (II) complexes in plasma ultrafiltrate. Anal Biochem 143: 46–56

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