More About: Irinotecan-Related Cholinergic Syndrome Induced by Coadministration of Oxaliplatin

Recently, Valencak et al. (1) reported an interesting observation relating to a cholinergic episode experienced by a patient receiving the combination of irinotecan and oxaliplatin in a phase II study. When irinotecan was given as a 1-hour infusion (80 mg/m²) at the end of the oxaliplatin 2-hour infusion (85 mg/m²), the patient had hypersalivation and abdominal pain. These symptoms resolved promptly with atropine and did
not recur when irinotecan was administered alone 1 week later. Similarly, administration of the two drugs 1 day apart did not give rise to the same symptoms. However, rechallenge with the two drugs with the original protocol again led to cholinergic toxicity.

These symptoms are typical of the acute syndrome experienced by some patients treated with irinotecan alone (2) and suggest that an interaction is occurring between the two drugs, with oxaliplatin potentiating the severity of irinotecan’s cholinergic side effects.

In response, Cvitkovic et al. (3) argued that this interaction is likely to be of little clinical significance because, in their hands at least, the irinotecan–oxaliplatin combination is safe and does not result in increased cholinergic toxicity. However, as Cvitkovic et al. pointed out, they administer atropine prophylactically to patients treated with this combination. Therefore, it is possible that the type of interaction reported by Valencak et al. (1) has been largely masked by atropine prophylaxis.

The lack of an obvious pharmacokinetic interaction between the two drugs (4) would suggest that the toxicity is the result of pharmacodynamic factors. The cholinergic effects of irinotecan have been suggested to be mediated through ganglionic stimulation by the bipiperidino moiety released when irinotecan is activated to SN-38 by esterases. However, we have demonstrated that irinotecan is a potent direct inhibitor of human acetylcholinesterase at clinically relevant concentrations (5). Indeed, the potency and kinetics of inhibition of irinotecan are very similar to those of tacrine (Dodds HM, Ollis DL, Rivory LP: unpublished observations). The important features of this inhibition are that it is rapidly reversible and more pronounced for the lactone form of irinotecan.

Potentiation of irinotecan’s inhibition of acetylcholinesterase by oxaliplatin, although requiring formal demonstration, is supported indirectly by studies demonstrating that several other alkylating drugs used in oncology (e.g., cisplatin and cyclophosphamide) are moderate inhibitors of human acetylcholinesterase (6,7). Although these drugs are not known to yield symptoms consistent with cholinergic toxicity in clinical use, a possible mechanism for a pharmacodynamic interaction is nevertheless evident.

Therefore, we agree with the conclusions of Valencak et al. (1) that this apparent interaction could be significant, particularly when atropine is not used prophylactically. Furthermore, the use of atropine in the development of other combinations containing irinotecan may mask similar occurrences of potentiated cholinergic toxicity, thereby preventing a complete characterization of their safety profiles.

HELEN M. DODDS
JAMES F. BISHOP
LAURENT P. RIVORY

REFERENCES


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Affiliations of authors: H. M. Dodds, The University of Queensland Department of Medicine, Princess Alexandra Hospital, Brisbane, Queensland, Australia; J. F. Bishop, L. P. Rivory, Medical Oncology, Sydney Cancer Centre, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia. Correspondence to: Laurent P. Rivory, Ph.D., Medical Oncology, Sydney Cancer Centre, Royal Prince Alfred Hospital, Camperdown, New South Wales 2050, Australia.