

Effect of Drugs on the Cardiac Transport, Metabolism and Action of Idarubicin: Pharmacokinetic and Pharmacodynamic Modeling

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Using the isolated perfused rat heart this study investigated 1) the cardiac uptake of idarubicin (IDA), 2) the role of P-glycoprotein (P-gp) in the uptake process, 3) the formation of IDOL from IDA in the heart, and 4) the effect of P-gp inhibitors (verapamil, amiodarone, PSC 833), doxorubicin, hypothermia, xanthine derivatives (caffeine, theophylline) and metabolism inhibitors (rutin, phenobarbital) on the pharmacokinetics and pharmacodynamics of IDA using a mathematical modeling approach. A minimal model was constructed; the differential equations were numerically solved and fitted to the data using the ADAPT II-software package using maximum likelihood estimation assuming that the measurement error has a standard deviation which is a linear function of the measured quantity [1].

For the first time, it is shown that the cardiac uptake of IDA and IDOL is saturable and that the uptake rate (V_{max}) is increased by P-gp inhibitors (verapamil and amiodarone), probably because of impairment of P-glycoprotein mediated influx hindrance. The evidence of a Michaelis-Menten like process is strongly supported by a noncompetitive inhibition of doxorubicin and uptake hindrance in hypothermic condition (increase of K_M). In addition, the combined kinetic-dynamic model provided further insight into the mechanism underlying the time course of the acute negative inotropic effect of anthracyclines [2]. Verapamil and amiodarone attenuate the acute negative inotropic action of IDA despite an increase of the penetration into the heart. PSC 833, in contrast, enhanced the recovery of IDA and IDOL formed from IDA but potentiated the IDA-induced increase in coronary vascular resistance [3].

The enhanced myocardial uptake of IDA in the presence of caffeine can be explained by an increased maximal rate of saturable uptake process (V_{max}). The clinical significance of this interaction is not clear, however, this result suggests that caffeine intake may increase the cardiotoxicity of IDA. Further studies are needed to resolve this question.

Rutin inhibits the generation of IDOL from IDA despite the enhancement of IDA accumulation probably because it also increases the sequestration of IDA, and represents a

beneficial vasodilating effect possibly due to an antioxidant property. While phenobarbital also decreases the formation of IDOL, but potentiates the IDA-induced vasoconstriction. The practical importance of a possible reduction of IDA-induced cardiotoxicity due to an inhibition of IDOL formation by rutin and phenobarbital is unclear, because only 2 % of IDA dose is transformed to IDOL in the heart for a 1-min infusion of IDA. However, the increase of IDOL formed with increasing infusion time should be considered.

These results may provide a better understanding of the cardiac pharmacokinetics and pharmacodynamics of IDA including the influence of other drugs on these processes. Thus, these findings may contribute to predict drug interactions in anthracycline chemotherapy. They may also be useful to optimize the dosing regimens and to improve strategies to overcome multidrug resistance with respect to cardiotoxicity of anthracycline.

References

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