Reply

Mechanisms of action of various ATP-sensitive potassium channel openers

David J. Hearse a, Icilio Cavero b

a The Rayne Institute, St. Thomas' Hospital, London SE1 7EH, UK
b Rhone-Poulenc Rorer, CRVA, Vitry sur Seine, France

Keywords: Potassium channel, ATP sensitive; Potassium channel openers

Dr. Grover’s very kind and complimentary remarks about the recent review [1] on ATP-sensitive potassium channel openers during ischemia and reperfusion are much appreciated. One point, however, causes Dr. Grover considerable concern—this is the citation of (and by implication a presumed agreement with) the comments in the paper by Richer et al. [2]. This paper was critical of the conclusions of a study [3] by Dr. Grover and colleagues in which the authors compared intravenous versus intracoronary administration of nicorandil versus cromakalim. This reply to Dr. Grover is from the author of the review [1] and the senior co-author of the contentious paper [2].

Dr. Grover states that “Professor Hearse criticised this study based on the 100-fold lower dose of nicorandil given into the coronary”. Dr. Grover then goes on to justify the choice of this dose on the basis of the fact that the coronary bed supplies a very small mass of tissue and therefore a much lower absolute dose is required than with intravenous administration. We fully accept this and indeed, neither the review [1] nor the Richer article [2] took specific issue with this aspect of Dr. Grover’s protocol design. The criticism that was intended related not to the choice of dose between intravenous and intracoronary studies but to the fact that Grover et al. [3] used a dose of nicorandil that was only 3 times higher than that selected for cromakalim. What Professor Hearse actually stated in his concluding synopsis of the Richer paper was that “they argued that, since nicorandil was ten times less potent than cromakalim, any study designed to compare the two drugs and the two routes of administration should have employed a larger dose of nicorandil.” The choice of intravenous versus intracoronary dose was not actually contested by the author of the review. The point at issue (which has been made on a previous occasion [4] by the co-signatory of this letter) is quite straightforward: namely, that because nicorandil is at least 10 times less potent than cromakalim as a potassium channel activator, then to make an appropriate comparison between the two compounds Dr. Grover should perhaps have used a larger relative dose of nicorandil. On the basis of this, it would seem to us that it is inappropriate to categorically claim that nicorandil fails to protect under conditions where cromakalim is effective. We are sure that Dr. Grover would agree that definitive conclusions about the failure of a drug to act should only be made after the completion of comprehensive dose–response studies—the failure to demonstrate efficacy is not always the fault of the drug!

The title of Dr. Grover’s paper [3] is: “Nicorandil improves post-ischemic contractile function independently [our italics] of direct myocardial effects”—the thrust of Dr. Grover’s arguments appear to be directed towards the conclusion that the protective effects of intravenous nicorandil must, at least in part, be attributed to peripheral effects of the drug. In order to accept this conclusion, it could be argued that the Dr. Grover should have demonstrated that glibenclamide (which should not influence the alleged peripheral nitrate-related protective effects of nicorandil) is unable to reduce the protective effects of intravenous nicorandil on cardiac contractile function. In this connection (and conflicting with Dr. Grover’s arguments), we would draw attention to the paper by Auchampach et al. [4] which suggests that the protective effects of nicorandil are fully mediated by potassium channel opening. In this study, it was shown that the protective properties of intravenous nicorandil in a stunning model (like that used by Dr. Grover) were fully prevented by glybenclamide at a dose that did not block the hemodynamic effects of nicorandil. We are therefore forced to ask Dr. Grover how intravenous nicorandil could protect the heart via its nitrate-like (preload and/or afterload) activity? In conclusion, while we do not dispute the fact that nicorandil has both cardiac and peripheral actions, at this time, it...
would seem to us that the protective effects of the drug on cardiac function can be adequately explained by its effects on cardiac ATP-sensitive potassium channels without any need to invoke an independent peripheral mechanism. As pointed out in the review [1], the profound protective effects of nicorandil in globally ischemic isolated hearts (where there can be no peripheral effect!) shows that nicorandil is able to exert a powerful effect independent of any direct vascular actions.

Finally, Dr. Grover claims that the review [1] made no mention of the fact that "nicorandil is an NO donor"—this is perhaps a little unfair since the nitrate moiety of nicorandil and its important secondary pharmacological effects on the vasculature were mentioned the very first time that nicorandil was discussed (section 3.2, lines 5 and 6) and on subsequent occasions (e.g., section 3.9. and particularly section 7.4 where the potential role for a nitrate-mediated mechanism was specifically discussed).

Although we felt obliged to respond in a spirited manner to the castigations of Dr. Grover, we do in fact fully support his philosophy that the interpretation of results must be carried out with the greatest of caution—hence the concerns that have been reiterated above and on other occasions [4].

References