

Effect of Picotamide on Prostacyclin Production by Human Endothelial Cells

Dear Sir,

Picotamide, a derivative of 4-methoxy-isophthalic acid, has been recently shown to inhibit thromboxane synthetase as well as thromboxane receptors in vitro and in vivo (1). Due to these effects the compound has a potential usefulness as antithrombotic agent (2). In order to further elucidate the pharmacological properties of picotamide we investigated the effect of this compound on PGI₂ production by cultured endothelial cells. Human endothelial cells, obtained from umbilical cords as described by Jaffe et al. (3), were grown in vitro and subcultured in 24-well cluster plates as previously described (4). To measure the effect of picotamide on PGI₂ production, endothelial cell monolayers were washed twice with Dulbecco buffered saline (DBS) and then incubated for 30 min at 37° C with 0.5 ml of DBS containing picotamide at final concentrations ranging between 1.5 and 390 µg/ml. This compound was added to DBS as ethanolic solution. Final ethanol concentration was 0.04% (w/v). At this concentration, and in a similar experimental set up, ethanol had been demonstrated to have a moderate stimulatory effect on PGI₂ production (4). In control experiments the same ethanol dose was thus used. At the end of incubation the supernatants were frozen and kept at -70° C until the assay could be performed. Concentrations of 6-keto-PGF_{1α} in the supernatants were assayed by radioimmunoassay. The effect of the various doses of picotamide on endothelial PGI₂ is reported in Table 1. No significant reduction of PGI₂ production was observed for picotamide concentrations up to 6 µg/ml. At higher picotamide concentrations the inhibition was dose-dependent up to 24 µg/ml where a 50% inhibition was achieved; higher picotamide concentrations caused a substantially similar PGI₂ decrease thus suggesting some

enzymatic non-competitive type inhibition. The degree of PGI₂ inhibition was not raised when the time of exposure of endothelial cells to the drug was increased. The effect of picotamide on PGI₂, although moderate, shows that the pharmacological properties of this compound are more complex than earlier recognized. It can be suggested that the inhibition of thromboxane synthesis, thromboxane receptors and PGI₂ synthesis might all derive from a more general effect of this molecule which requires further studies in order to be elucidated. In considering picotamide as potential antithrombotic agent, it has to be remarked that the inhibition of PGI₂ observed in vitro is moderate and requires picotamide levels much higher than those achieved in vivo following oral administration. On this basis it is possible that the use of appropriate doses of picotamide in vivo could allow to block thromboxane synthesis and thromboxane effect without affecting PGI₂.

Yours sincerely

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References

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Table 1 Effect of picotamide on endothelial PGI₂

Picotamide dose (µg/ml)	6-keto-PGF _{1α} (% of control)*
1.5	103
3	105
6	95
12	75
24	52
48	47
192	48
384	44

* Results of three individual experiments are listed.

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