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*Commentary*

# Flavone Acetic Acid—Preclinical and Clinical Activity

D.J. KERR* and S.B. KAYE

*CRC Department of Medical Oncology, 1 Horselethill Road, University of Glasgow, Glasgow G12 9LX, U.K.*

THE FLAVONOID AGLYCONES, widespread in photosynthesizing plants, have been used in empirical medical praxis for centuries to treat conditions as varied as rheumatoid arthritis and bee stings. Two synthetic flavonoid compounds have recently undergone phase I/II tests in cancer patients. The first, an ester of flavone acetic acid (FAA) and diethylethanolamine (coded LM985), proved to be a relatively toxic prodrug of FAA with acute hypotension as its dose limiting toxicity [1]. This compound did not go forward to phase II trials.

FAA has an impressively wide spectrum of preclinical activity which includes relatively refractory and slow growing murine tumours such as colon 38, pancreatic adenocarcinoma and Glasgow's osteogenic sarcoma [2]. Detailed pharmacokinetic studies were performed and correlated with toxicity and antitumour effect. There appears to be a therapeutic window in mice with antitumour effects at plasma concentrations >100 μg/ml and toxicity at concentrations in excess of 600 μg/ml. The 'therapeutic window' is 2-dimensional in the sense that infusional studies have shown that prolonged exposure (more than 24 h) within the window can be associated with toxicity [3]. A phase I trial of FAA, conducted in tandem with a pharmacokinetic study, was undertaken in our department [4]. Two schedules were tested and hypotension, diarrhoea and flushing were found to be dose limiting. Recommended phase II schedules were 4.8 g/m$^2$ over 1 h and 8.6 g/m$^2$ over 6 h. End of infusion peak plasma concentrations were well within the murine therapeutic window (respectively 650 and 388 μg/ml), however the amount of 'effective' drug delivered (which we defined as the AUC greater than 100 μg/ml for plasma concentration time curves) was greater for 8.6 g/m$^2$ over 6 h than for the 1 h schedule (2852 μg/ml.h vs. 1885 μg/ml.h). FAA has non-linear pharmacokinetics [5] and it is likely that the rate limiting step in its metabolism and distribution occurs during extensive hepatic metabolism to glucuronides [6].

Phase II trials of FAA have hitherto been negative. The Early Clinical Trials Group of the EORTC tested 4.8 g/m$^2$ and found no activity in cancers of the breast, colon, lung, head and neck and melanoma [7]. The Cancer Research Campaign Phase II clinical trials group found that 8.6 g/m$^2$ over 6 h was inactive in advanced malignant melanoma and colorectal carcinoma [8].

Therefore, despite impressive preclinical activity, FAA has been found hitherto to be clinically inactive. The disappointed clinician asks why and what does the future hold for this class of compounds? There are two broad areas which can be explored to seek an explanation for its inactivity. Pharmacokinetic differences exist comparing mouse and man. FAA is metabolized in man to glucuronides and has a far higher plasma clearance than in mice. FAA is more tightly plasma protein bound in man, therefore reducing the amount of free drug in plasma water available for diffusion to its site of action. Studies from our laboratory [9] have shown that the concentration of free drug in plasma in mouse and man is similar at maximum tolerated doses. Relating this to the 'therapeutic window' concept it is possible that the duration of exposure above the threshold concentration is greater in mice due to decreased plasma clearance. However the magnitude of this

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*To whom requests for reprints should be addressed.

effect alone would be unlikely to be great enough to explain the lack of efficacy of FAA.

The mechanism of action of FAA is uncertain. It causes single strand breaks in the DNA of treated cells, but the degree of DNA damage is minimal and unlikely to contribute significantly to its cytotoxic effect [10].

Although FAA has direct cytotoxic effects *in vitro*, it has fascinating effects on tumour blood flow in the intact animal. Smith *et al.* [11] have shown that FAA can induce striking haemorrhagic necrosis in murine colonic tumours growing subcutaneously. Recently elegant studies [12] have demonstrated that FAA depletes ATP concentrations in tumours, and that this effect is mediated by a reduction in tumour blood flow. In that study, tumour blood flow was measured by $^{31}P$ nuclear magnetic resonance spectroscopy. It is tempting to correlate the experimental behaviour of FAA with its clinical toxicity, namely hypotension. However, no tumour responses were seen even in those patients who had significant hypotension (>20 mmHg drop in systolic or diastolic pressure). It would be reasonable to argue that changes in peripheral blood flow/blood pressure do not reflect changes in tumour blood flow and specific studies aimed at delineating the effect of FAA on tumour blood flow in patients would perhaps help to select subgroups who might respond.

FAA has effects on host immune systems and can augment systemic natural killer cell activity in normal and tumour bearing mice and in human cancer patients. There is some evidence to suggest that these effects are mediated by induction of α and/or β interferon [13].

Despite clinical inactivity FAA remains an interesting lead compound and possible routes for further clinical development could include synthesis of analogues, combination with lymphokines such as interleukin II and studies aimed to assess its effects on tumour blood flow *in vivo*.

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