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Flavone acetic acid (LM 975, NSC 347512) A novel antitumor agent*

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Summary. Flavone acetic acid (FAA) is a synthetic flavonoid compound which has recently begun clinical trials as an antitumor agent based on its striking activity in solid tumor model systems. The pharmacologic behavior of FAA in animals appears to be predictive of both its cytotoxic efficacy and its toxicity to normal tissues (principally the central nervous system and gastrointestinal tract). The design and conduct of phase I studies in man are based upon these principles, with the goal of maximizing their safety and efficacy.

Introduction

Flavone acetic acid (FAA, LM 975, NSC 347512) is a synthetic flavonoid compound synthesized in France by Lipha Pharmaceuticals. Its novel structure and unusual spectrum of activity in preclinical solid tumor models has led to its introduction into phase I clinical trials in the United States of America. Another member of the flavone family, the diethylaminoethyl ester derivative of FAA (NSC 293015), has been studied in a phase I trial in Europe. The rapid hydrolysis of the ester to FAA allows a preliminiary estimate to be made of the pharmacology of FAA in humans. In this paper we review the pharmacology of FAA in several species, relate this to findings in rodent antitumor and toxicology studies, and indicate appropriate schedules for phase I study in humans.

Chemistry and formulation

Flavonoids comprise a family of naturally occurring compounds widely distributed in photosynthesizing cells [6]. Flavonoids have been shown to inhibit several mammalian enzymes. Those likely to be inhibited by the benzopyrone ring structure include ATPases, cAMP phosphodiesterase, aryl hydroxylase, aldose reductase, and proline hydroxylase [6]. Flavones, a class of flavonoids, are 2-phenyl-4*H*-l-benzopyran-4-ones; flavone acetic acid is a simple derivative of this basic structure (Fig. 1). Flavone was shown to have potent smooth muscle relaxing properties in 1952 [7]. A flavone derivative currently in use in the clinic is flavoxate (piperedeno-ethyl-3-methylflavone-8-carboxylate), an antispasmodic agent for the relief of bladder irritability. Flavoxate and its major metabolite 3-methylflavone-8-carboxylic acid (MFCA) are potent inhibitors of phosphodiesterase (21 and 5 times more potent than theophylline, respectively) [4]. In addition, Cazzulani et al. [2] found flavoxate to have calcium antagonist activity (approximately 10 times that of verapamil), and local anesthetic activity similar to lidocaine; however, MFCA did not retain these characteristics, which are therefore not thought to reside in the flavone moiety.

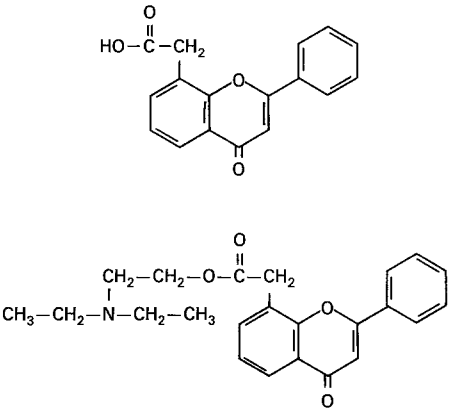

Fig. 1. Structure of FAA *(top)* and the diethylaminoethyl derivative of FAA *(bottom)*

Another flavonoid in development, quercetin, has among its many actions an antitumor-promoting activity which appears to be mediated through a calcium antagonist effect [9]. Future work with quercetin may help elucidate the basis for the cytotoxicity of FAA although a close analogue of quercetin does not have activity against the colon 38 tumor[1].

FAA is a white powder soluble (>20 mg/ml) in dimethyl sulfoxide and in 0.1 *N* NaOH but less soluble in methanol or in ethanol (about 1 mg/ml) and in other solvents (0.1 *N* HCl and chloroform <0.1 mg/ml). Solubility of FAA is markedly influenced by pH. Although solubility in water is about 6 µg/ml, adjustment to pH 7–9 increases solubility to 20–50 mg/ml. FAA is formulated as a sterile, freeze-dried dosage form containing 250 mg of the drug and sodium hydroxide to yield the sodium salt. Continu-

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ing studies indicate that the freeze dried product is stable for 6 months at 50 °C, room, and refrigeration temperatures. While these studies continue, refrigeration (2°–8 °C) is the recommended storage temperature.

Constitution of the dosage form with 10 ml of sterile water for injection, USP, provides a 25 mg/ml solution of FAA, pH 7–9, that is chemically stable for 14 days at room temperature. More concentrated solutions can be prepared by addition of 2.4 or 4.8 ml of the same diluent to yield 100 and 50 mg/ml, respectively of FAA. The drug is chemically stable at these concentrations for at least 24 h but may precipitate if stored under refrigeration. Further dilution of the constituted solution to 0.5 mg/ml with sodium chloride injection, USP, provides a clear solution that exhicits only 2%–3% loss over 14 days at room temperature. However, dilution to the same concentration with 5% dextrose injection, USP, results in drug precipitation, presumably due to the low pH of this infusion fluid. Prior addition of sodium bicarbonate injection 4 mEq/100 ml 5% dextrose for injection, USP, prevents precipitation; this solution also exhibits 2%–3% loss over 14 days at room temperature. Since these FAA solutions do not contain antibacterial preservatives, they should be used within 8 h after preparation. Low aqueous solubility of FAA suggests that crystallization of the compound may occur in acidic body fluids (i.e., urine), particularly after administration of high doses. Methotrexate exhibits similar behavior, and bicarbonate is recommended in high-dose regimens to alkalinize urine. Current NCI approved protocols for FAA also include this recommendation.

Antitumor activity

Flavone acetic acid was selected for development to clinical trial based on its activity against the s. c. implanted murine colon adenocarcinoma 38. This tumor as used in the NCI tumor panel has been refractory to most compounds tested. An analysis of the data in mid-1982 indicated that only 2.3% of the 1708 compounds tested inhibited tumor growth by 90%–100%. The majority of the compounds tested had been selected because they had demonstrated some level of activity [increase in life span (ILS) $\geq$20%] against the i.p.-impalnted P388 leukemia, but some were selected on the basis of other properties believed to be relevant to antitumor activity. Of the 39 compounds active against colon adenocarcinoma 38, only 1 was inactive against the P388 leukemia. The parent flavone acetic acid ester was one of the compounds selected on the basis of activity against P388 leukemia, producing optimal ILS values of 98% and 38% following i.p. administration on days 1–9. FAA was tested after the 1982 analysis, was active against the colon adenocarcinoma 38 following i.v. or i.p. administration on days 2 and 9 and demonstrated no anti-P388 leukemia activity in the initial experiment conducted using the same treatment regimen employed for the ester. Thus, at the time of its selection, FAA demonstrated an unusual spectrum of activity: good activity against the colon 38 tumor, none against the P388 leukemia (in later experiments activity against P388 leukemia was demonstrated).

The effect of the treatment schedule on the activity of i.p.-administered FAA against the s.c.-implanted colon adenocarcinoma 38 was examined using both early- and late-stage tumor [11]. When treatment was initiated on day 2, FAA apparently demonstrated reduced therapeutic efficacy when the interval between treatments was reduced to 3 h, even though the mice tolerated a greater total dose than those receiving a single injection of the drug. An 84 mg/kg dose administered every 3 h for a total of four injections (total dose 336 mg/kg) caused complete inhibition of tumor growth in only 3/10 or 1/10 mice, depending on the day of evaluation (days 20 and 60, respectively). By comparison, a single treatment on day 2 with a 200 mg/kg dose produced 9/10 and 8/10 tumor-free survivors on days 20 and 60, respectively, and two 150 mg/kg treatments 6 h apart produced 7/10 and 6/10 tumor-free survivors on the same evaluation days. With a single drug injection per day, two courses of treatment given 7 days apart yielded therapeutic results equivalent to those of a single course. Similarly, when treatment was delayed until the tumors weighed approximately 500 mg (day 14), no marked difference in efficacy was observed with either a single treatment or two treatments 6 h or 7 days apart [11]. However, reduced antitumor activity, as determined by the number of tumor-free survivors on day 100 and tumor regrowth delay, was noted with two chronic schedules (daily $\times 5$ and daily $\times 9$). Although the total doses administered were greater on the chronic schedules, individual doses tolerated were smaller.

As mentioned above, FAA demonstrated no activity in the initial experiment conducted with the i.p.-implanted P388 leukemia model using a treatment regimen of i.p. administration on days 1–9. However, additional studies have indicated that under the right conditions P388 leukemia is sensitive to FAA. In early testing, a 100 mg/kg dose administered as a suspension in saline allowed tumor cell populations to increase by approximately 0.2–1.9 $\log_{10}$ units during treatment (three experiments). In contrast, tumor burden during treatment was reduced by 1.5–3 $\log_{10}$ units in three of four experiments and the median life span of the mice was increased by 108%–128% when a 100 or 150 mg/kg dose of FAA was administered as a solution in sodium bicarbonate.

Activity was also observed in the other tumor models routinely used by the NCI screening program (Table 1). Against the i.p.-implanted B16 melanoma, FAA produced maximum ILS values of 109%, 72% and 52% in three experiments following i.p. administration on days 1–9. Using the same treatment schedule, moderate activity (ILS values = 47% and 35%) was demonstrated in two of three experiments with the i.p.-implanted L1210 leukemia model. However, FAA was not effective against the L1210 leukemia (or P388 leukemia) when administered as a single treatment on day 1. Thus, with the more rapidly dividing leukemias, a single treatment (sodium bicarbonate used as vehicle for FAA administration) does not appear to be sufficient to elicit a significant therapeutic response (based on limited testing). The highly metastatic human LOX amelanotic melanoma was responsive to FAA; the life span of athymic mice bearing the i.p.-implanted tumor was increased by 119% following i.p. treatment on days 1, 5, and 9. Two other human tumor xenografts (MX-1 mammary and CX-1 colon) evaluated in the sub-renal capsule assay did not respond to FAA.

Additional studies were conducted at Wayne State University [5]. Moderate to good antitumor activity was demonstrated against the colon adenocarcinomas 07/A, 51, and 10A, the undifferentiated colon carcinoma 26, the

Table 1. Spectrum of preclinical antitumor activity of FAA

Tumor system	Treatment schedule	Activity rating[a]
Murine leukemias		
i.p. L1210	i.p. Q1D, days 1–9	+
i.p. P388	i.p. Q1D, days 1–9	+/++[b]
	i.p. Q1D, day 1 only	–
Murine solid tumors		
i.p. B16 melanoma	i.p. Q1D, days 1–9	++
s.c. Colon adenocarcinoma 38	i.p. Q7D, days 2, 9	++
	i.v. Q7D, days 2, 9	++
s.c. Colon adenocarcinoma 07/A	i.v. Q7D, days 11, 19	++
s.c. Colon adenocarcinoma 10/A	i.v. Q7D, days 7, 14, 21	++
s.c. Colon adenocarcinoma 51	i.v. Q4D, days 3, 7, 11, 15	++
s.c. Colon carcinoma 26	i.v. Q3D, days 2, 5, 8, 11	+
s.c. Pancreatic ductal adenocarcinoma 03	i.v. Q4D, days 3, 7, 11	++
s.c. Pancreatic ductal adenocarcinoma 02	i.v. Q4D, days 3, 7, 11	+
s.c. Mammary adenocarcinoma 16/c/adr	i.v. Q2D, days 4, 6, 8	+
s.c. Osteogenic Sarcoma (^{239}Pu-induced)	i.v. Q6D, days 2, 9, 14	++
s.c. M5076 Sarcoma	i.v. Q5D, days 3, 8, 13, 18, 23	++
Human tumor xenografts		
s.r.c. CX-1 Colon tumor	i.p. Q4D, days 1, 5, 9	–
s.r.c. MX-1 Mammary tumor	i.p. Q4D, days 1, 5, 9	–
i.p. LOX Amelanotic melanoma	i.p. Q4D, days 1, 5, 9	++

[a] Activity: ++ ≥50% ILS for i.p. tumors (≥75% for P388);
≥90% inhibition of tumor growth for s.c.- and S.r.c.-implanted tumors
+ 25%–49% ILS for i.p. tumors (27%–74% for P388);
58%–89% and 80%–89% inhibition of tumor growth for s.c. and s.r.c. tumors, respectively

[b] Single + activity rating based on FAA administered as a suspension in saline, double rating obtained with FAA solubilized in warm 2% sodium bicarbonate

pancreatic ductal adenocarcinomas 02 and 03, mammary adenocarcinoma 16/C/Adr, M5076 ovarian tumor, and a plutonium-induced osteogenic sarcoma (Table 1). All these tumors were implanted s.c. The treatment schedule for each tumor system is shown in Table 1. For single-dose bolus administration, antitumor efficacy was proportional to dose. Splitting the dose invariably reduced the activity in a "threshold" manner [5]. However, short infusion schedules were active. Against the pancreatic ductal adenocarcinoma 03, a dose of 435 mg/kg by 24-h infusion resulted in cures in 6/7 mice. A dose of 260 mg/kg by 24-h infusion resulted in less activity than a 117 mg/kg i.v. bolus dose (T/C = 35% vs T/C = 57%) and far less than a 174 mg/kg i.v. bolus dose (T/C = 0%). Hence the total dose of FAA was not a major determinant of antitumor effect. The activity was better correlated with the production of mild but evident toxicity characterized as stupor and with a probable plasma threshold level. Therefore, in agreement with the NCI results, intermittent bolus or short infusion schedules repeated every 4 or 7 days appeared to be optimal.

Toxicology

Preclinical toxicology studies were conducted in $CD2F_1$ mice, beagle dogs, and Fischer 344 rats. Acute toxicity studies in the mice were performed using schedules of single dose (×1) and five consecutive daily doses (×5). Death occurred on day 2 in mice on the ×1 schedule with the exception of a single female in the 1050 mg/m^2 group, which died on day 3. Death occurred between days 2 and 6 on the ×5 schedule. The toxic signs observed included convulsions, lethargy, decreased activity, rough hair coat, hunched posture, emaciation, and discharge from the eyes. The combined sex lethal dose values LD_{10}, LD_{50}, and LD_{90}, were 1029, 1176 and 1347 mg/m^2, respectively, for the ×1 dose scheule and 360, 417, and 486 mg/m^2 per day, respectively, for the ×5 schedule.

Intravenous administration of FAA to beagle dogs produced toxicity to the gastrointestinal system with single doses of 4000 mg/m^2 ($4 \times MELD_{10}$)[2], 2000 mg/m^2 ($2 \times MELD_{10}$), and 1000 mg/m^2 ($MELD_{10}$) and to the gastrointestinal and the nervous system on the ×5 dose schedule at 1440 mg/m^2 per day ($4 \times MELD_{10}$) and 360 mg/m^2 per day ($MELD_{10}$). No drug-related mortalities occurred, and all toxicities were reversible. Gastrointestinal toxicity consisted of emesis, diarrhea, soft stools, and hypersalivation. Nervous system toxicity consisted of tonic convulsions, pedalling, loss of bladder control, relaxation and/or depression, tremors, and muscle weakness. No drug-related gross or microscopic lesions were observed.

Since no lethality was observed in the dogs at $4 \times MELD_{10}$ on either schedule, limited range-finding studies were also performed. On the ×1 schedule, three dogs were treated at 7000, 10–000, and 12–000 mg/m^2 ($7 \times MELD_{10}$, $10 \times MELD_{10}$, and $12 \times MELD_{10}$). Severity of response was dose-dependent and consisted of emesis, muscle weakness, decreased activity, constricted pupils, and swollen eylids, all of which returned to normal on day 2. Renal and hepatic effects (increases in alkaline phosphatase, BUN, SGOT, and SGPT) returned to normal on

[2] $MELD_{10}$ = Mouse equivalent LD_{10}, the dose which is lethal to 10% of a cohort of treated mice. This dose may be extrapolated across species if calculated according to surface area

day 8. The dog treated at the highest dose ($12 \times MELD_{10}$) showed a slight increase in white blood cells and mature neutrophils and a decrease in lymphocytes on day 2 as well as moderate decreases in chloride and potassium concentrations. On the $\times 5$ schedule two dogs were dosed at 2520 mg/m^2 per day ($7 \times MELD_{10}$) and 4320 mg/m^2 per day ($12 \times MELD_{10}$). The dog treated at the lower dose experienced repeated emesis during all days of treatment and showed signs of weakness and low food consumption. The dog treated with the higher dose demonstrated tonic convulsions with vocalization, loss of bladder and anal sphincter control, jaw movement, hypersalivation, and repeated emesis, as well as signs of weakness and soft stools.

In toxicology studies with rats, lethality occurred in 5/10 females and 4/10 males by day 2 after a single i.v. injection of FAA at $2 \times MELD_{10}$ (2064 mg/m^2). Drug-related toxicity at this dose was observed in the nervous, hematologic, endocrine, lymphatic, gastrointestinal, and hepatic systems. The nonlethal, drug-related toxicities were reversible, and were only observed on this high-dose,single-injection treatment. Single doses of 102 mg/m^2 ($1/10MELD_{10}$) and 1032 mg/m^2 ($MELD_{10}$), as well as the $\times 5$ schedule at 36 mg/m^2 per day ($1/10MELD_{10}$), 360 mg/m^2 per day ($MELDs_{10}$), and 720 mg/m^2 per day ($2 \times MELD_{10}$) produced no observable drug-related toxicity. Hence, the toxicities to be anticipated in humans include neurologic and gastrointestinal toxicity.

Pharmacology

The pharmacokinetics of FAA have been studied in mice and dogs [13], and the plasma disappearance curve of FAA following i.v. administration of the diethylaminoethyl ester to man has been described [8]. Analyses were performed with a sensitive high pressure liquid chromatography method. Following the administration of 600 mg/m^2 i.v. to mice, plasma levels fit a monoexponential decay curve with a half-life of 4.85 h [13]. Plasma clearance was 80 ml/h per kg and V_D was calculated to be 0.54 l/kg. Evidence for nonlinear kinetics in the therapeutic range has been published [1, 3]. Contrary to the experience with most drugs, dogs cleared FAA more rapidly than mice [13]. Plasma clearance was double that in the mouse (143 ml/h per kg) and V_D was 0.30 l/kg (Table 2). The terminal half-life following an i.v. dose of 4000 mg/m^2 in dogs was 4.8 h, and plasma disappearance followed a biexponential curve. Similar results were obtained in another study in which CSF levels close to plasma levels were observed at 30–60 min [10]. Toxic doses in each species yielded similar concentration-time products, suggesting that the area under the curve (AUC) is an important determinant of toxicity [1, 13].

Indirect evidence of the pharmacologic behavior of FAA in humans is obtained from a phase I study of its diethylaminoethyl ester [8]. Rapid hydrolysis of the ester to FAA occurs in plasma: the process is temperature-dependent and is abolished by heat-inactivation of the plasma. At doses of FAA-ester of 300–1500 mg/m^2, plasma levels of the ester and the acid fit a two-compartment model. The terminal half-life of the ester was 0.85 h, and that of the acid 2.2 h. Urinary excretion of unchanged drug was 12.5% of the administered dose. Peak plasma levels of FAA in mice that received 600 mg/m^2 of FAA ester i.v. were 326 μg/ml. Levels in humans were much lower than this (26 μg/ml after a dose of 1500 mg/m^2 of the ester). These data have implications for the toxicity and the anticipated antitumor activity of FAA, as will be discussed below.

In summary, the considerable interspecies differences in the pharmacology of FAA are unusual in that plasma clearance is more rapid in humans than in dogs and mice. More extensive study of routes of administration and extent of metabolism is needed to relate those observations to toxic effects. Clinical trials of FAA will use a dose escalation schema based on the preliminary pharmacokinetic observations.

Discussion

FAA is a novel structure with excellent antitumor activity in a variety of solid tumor models. Its mechanism of cytotoxicity is unknown. While its planar structure might suggest a potential for DNA intercalation, naturally occurring and synthetic analogues have been shown to inhibit a wide range of membrane-associated and cytosolic enzyme systems.

The pharmacokinetics of FAA have been described in mice and dogs. Plasma clearance is more rapid in the latter, and indirect evidence from clinical trials of FAA-ester suggest that the half-life in man will be even shorter. Studies in mice indicate that achievement of a critical plasma level of FAA (150–500 μg/ml) is required for optimal antitumor activity in solid tumor models [10]. At these levels, mice exhibited signs of reversible neurotoxicity, principally lethargy. Hence the drug may have a narrow therapeutic index, but mild CNS toxicity may provide a marker for therapeutic levels.

Toxicity has also been related to plasma levels in the dog. In this species too, neurotoxicity is dose-limiting. Plasma steady-state levels in the therapeutic range were achieved by a continuous infusion at two levels [13]. Equal toxicity was generated at equal $C \times T$ integrals, although steady-state plasma levels differed. Hence $C \times T$ is a reliable predictor of FAA toxicity in these species. Peak levels may also be important in humans however: in the study of FAA ester, hypotension was abolished by prolonging the infusion time.

These data have guided the design of phase I studies in humans. Owing to the interspecies pharmacokinetic differences, escalation of doses from the mouse-based starting dose ($1/10\ MELD_{10}$) will be more rapid than usual. There-

Table 2. FAA – Pharmacokinetics

Species	Dose (mg/m^2	Co	$t_{1/2}$ (h)	V_D (1/kg)	AUC	Clearance (mg/h per kg)
Mouse	600	368	4.85	0.54	2495	80
Dog	4000	675 M	0.9 4.8	0.30	1400	143

fore, fewer patients will be treated at low doses which are likely to be subtherapeutic. On reaching a maximally tolerated dose, by 1-h infusion, schedule manipulation will be attempted with the goal of reproducing the conditions which showed maximal antitumor efficacy in mice.

The schedules chosen for phase I study in man are based on the antitumor studies in mice. FAA is not highly schedule-dependent, and a single dose is superior to divided doses in all tumors tested. However, two doses spaced at a 1-week interval are superior to one. The schedules for phase I development in humans will include (a) single dose every 3 weeks, (b) single dose weekly $\times 3$, and (c) 24-h infusion. The last is based on the short half-life of FAA in man in contrast to the murine models in which the effect of schedule was tested.

In summary, detailed pharmacologic studies in preclinical models in association with specific antitumor activity and toxicology protocols provide a rational basis for the better development of FAA in the clinic. Further preclinical-clinical interaction during the course of clinical trials is expected to refine optimal delivery of FAA to maximize the probability of therapeutic efficacy.

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