Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions

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Flucytosine (5-FC) is a synthetic antimycotic compound, first synthesized in 1957. It has no intrinsic antifungal capacity, but after it has been taken up by susceptible fungal cells, it is converted into 5-fluorouracil (5-FU), which is further converted to metabolites that inhibit fungal RNA and DNA synthesis. Monotherapy with 5-FC is limited because of the frequent development of resistance. In combination with amphotericin B, 5-FC can be used to treat severe systemic mycoses, such as cryptococcosis, candidosis, chromoblastomycosis and aspergillosis. Recently, 5-FC has been combined with newer azole antifungal agents; it also plays an important role in a new approach to the treatment of cancer. The severe side effects of 5-FC include hepatotoxicity and bone-marrow depression. In most patients, these side effects are concentration dependent, predictable, possibly avoidable with close monitoring to maintain 5-FC concentrations at <100 mg/L, and reversible with drug discontinuation or reduction of dose. 5-FC is well absorbed after oral administration, penetrates into body tissues well and is excreted mainly by the kidneys. In renal failure, major dose adjustments have to be made. The most important drug interaction of 5-FC occurs with concomitant administration of 5-FC and nephrotoxic drugs, especially amphotericin B. Owing to the crucial role of glomerular filtration in 5-FC elimination, drugs that impair this mechanism will decrease the elimination of 5-FC and thus prolong its half-life.

Introduction

The treatment of deep-seated or systemic fungal infections has become more complex for a number of reasons. The range of clinically important fungi has broadened as a result of changes in medical care and international travel. In addition, the number of immunosuppressed patients and the prevalence of resistance to antifungal agents are both increasing.\textsuperscript{1}

One of the oldest antifungal agents is 5-fluorocytosine (flucytosine; 5-FC), a fluorinated analogue of cytosine. 5-FC was synthesized in 1957, as a potential anti-tumour agent\textsuperscript{2} but it was not sufficiently effective against tumours.\textsuperscript{3} Four years later, 5-FC proved to be active in experimental candidosis and cryptococcosis in mice\textsuperscript{4} and, in 1968, it was used to treat human candidosis and cryptococcosis.\textsuperscript{5} In addition to its activity against \textit{Candida} spp. and \textit{Cryptococcus neoformans}, 5-FC is active against fungi causing chromoblastomycosis.\textsuperscript{6}

Interest in 5-FC has been renewed as a result of two recent developments: (i) it is now used increasingly in combination with a number of azole antifungal agents, such as ketoconazole, fluconazole and itraconazole; (ii) it plays an important role in a new therapeutic approach in the treatment of certain tumours, especially colorectal carcinoma.

In this article, we review the pharmacology, pharmacokinetics, clinical indications, toxicity and drug interactions of 5-FC. Recent developments in the use of 5-FC are discussed, focusing on the combinations of 5-FC withazole antifungal agents. The possible role of 5-fluorouracil (5-FU) in the toxicity of 5-FC is explored and evaluated.

Mechanism of action

5-FC itself has no antifungal activity; its antimycotic activity results from the rapid conversion of 5-FC into 5-FU (Figure 1) within susceptible fungal cells.\textsuperscript{6-8} 5-FC is taken...
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up by these cells by the enzyme cytosine permease, which is also the transport system for adenine, hypoxanthine and cytosine. The latter compounds competitively antagonize the uptake of 5-FC. This carrier system is energy-dependent and coupled to a proton gradient. Once inside the fungal cell, 5-FC is rapidly deaminated to 5-FU by means of the enzyme cytosine deaminase. The specificity of this step is crucial for the narrow antifungal spectrum of 5-FC. Fungi lacking cytosine deaminase are not sensitive to 5-FC, since no conversion to the active metabolite takes place.

5-FU, on the other hand, cannot be used as an antimycotic drug, since it is highly toxic to mammalian cells and also because it is only poorly taken up by fungal cells.

After uptake of 5-FC into the fungal cell and conversion into 5-FU, two mechanisms can be distinguished by which 5-FU exerts its antifungal activity (Figure 2). The first mechanism involves the subsequent conversion of 5-FU through 5-fluorouridine monophosphate (FUMP) and 5-fluorouridine diphosphate (FUDP) into 5-fluorouridine triphosphate (FUTP). FUTP is incorporated into fungal RNA in place of uridylic acid; this alters the aminoacylation of tRNA, disturbs the amino acid pool and inhibits protein synthesis. The second mechanism is the metabolism of 5-FU into 5-fluorodeoxyuridine monophosphate (FdUMP) by uridine monophosphate pyrophosphorylase. FdUMP is a potent inhibitor of thymidylate synthetase, which is a key enzyme in the biosynthesis of DNA, since thymidylate synthetase is a crucial source of thymidine. Consequently, fungal DNA synthesis is inhibited.

It is not clear whether these two different pathways of 5-FC activity are equally important for the total antifungal effect of 5-FC. Using 5-FC-susceptible Candida albicans strains, it has been shown that there is a positive correlation between the degree of 5-FC susceptibility and the inhibition of both RNA and DNA synthesis, incorporation of 5-FU into RNA, inhibition of ribosomal protein synthesis and levels of FdUMP. However, some C. albicans strains have a reduced incorporation of 5-FU or reduced FdUMP concentrations, suggesting that these two pathways are not necessarily linked to each other and that both may be responsible for 5-FC activity. Despite these findings, there is controversy about the importance of the inhibition of fungal DNA synthesis by 5-FC.

Spectrum of antifungal activity and resistance

Spectrum of antifungal activity

5-FC is most active against yeasts, including Candida, Torulopsis and Cryptococcus spp., and against the dematiaceous fungi causing chromomycosis (Phialophora and Cladosporium spp.) and Aspergillus spp. The MICs of 5-FC vary from 0.1 to 25 mg/L for these fungal species.

In Emmonsia crescens, Emmonsia parva, Madurella mycetomatis, Madurella grisea, Pyrenochaeta romeroi, Cephalosporium spp., Sporothrix schenckii and Blastomyces dermatitidis, MICs vary from 100 to 1000 mg/L. 5-FC is also active against some protozoa, including Acanthamoeba culbertsoni both in vitro and in vivo and Leishmania spp. in patients.

Figure 1. Chemical structures of (a) cytosine, (b) flucytosine and (c) 5-fluorouracil.

Figure 2. Intracellular pathway and mode of action of 5-fluorouracil. Abbreviations: 5-FC, flucytosine; 5-FU, 5-fluorouracil; FUMP, 5-fluorouridine monophosphate; FUDP, 5-fluorouridine diphosphate; FUTP, 5-fluorouridine triphosphate; FdUMP, 5-fluorodeoxyuridine monophosphate.
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The mode of action of 5-FC and the essential role of cytosine deaminase have been proven in Saccharomyces cerevisiae and C. albicans and are probably also valid for other sensitive fungi.14 However, specific research in this field is lacking.

Resistance

The occurrence of resistance with the use of 5-FC has been widely described and precludes use of 5-FC as a single agent.5,11,17 Two basic mechanisms of resistance can be distinguished: (i) certain mutations can result in a deficiency in the enzymes necessary for cellular transport and uptake of 5-FC or for its metabolism (i.e. cytosine permease, uridine monophosphate pyrophosphorylase or cytosine deaminase);12,18 (ii) resistance may result from increased synthesis of pyrimidines, which compete with the fluorinated antimetabolites of 5-FC and thus diminish its anticyclosine activity.12 It has been shown that defective uridine monophosphate pyrophosphorylase is the most frequently occurring type of acquired 5-FC resistance in fungal cells.19

Normark & Schönebeck have reported that two different phenotypes of 5-FC-resistant strains can be recognized:17 strains of resistance phenotype class 1 are not affected by 5-FC at high concentrations (these are the totally (intrinsically) resistant strains), while those of class 2 are susceptible to 5-FC at low concentrations but, after long exposure to 5-FC (even at high concentrations) resistance develops (these are said to be partially resistant or to have acquired resistance). Development of resistance in the latter strains probably results from selection of non-susceptible mutants, leading to a secondary resistant population.12,14

The incidence of resistance to 5-FC varies between species.20 Up to 7–8% of intrinsically resistant strains are found among pretreatment isolates of C. albicans, unselected candida and Torulopsis glabrata. In C. neoformans the incidence of resistance is lower (1–2%), but in Candida spp. other than C. albicans it is 22%, because of the prevalence of generally less sensitive species such as Candida tropicalis and Candida krusei.20 The exact incidence of primary 5-FC resistance is not clear. Different investigators report rates ranging between 8% and 44% for Candida spp.21 Possible factors contributing to this wide range include the susceptibility methods used, local factors involving use of anti-fungal agents and differences in the prevalence of various Candida spp.21

Pharmacokinetics and dosing

The pharmacokinetics of 5-FC have been investigated and reviewed extensively.14,22 5-FC is absorbed very rapidly and almost completely: 76–89% is bioavailable after oral administration.23 In patients with normal renal function, peak concentrations are attained in serum and other body fluids within 1–2 h.22,23 5-FC penetrates well into most body sites, including cerebrospinal, vitreous and peritoneal fluids, and into inflamed joints, because it is small and highly water-soluble and is not bound by serum proteins to a great extent.7,22,24–27 5-FC is principally eliminated by the kidneys and the plasma clearance of the drug is closely related to creatinine clearance.7,22,24,27 5-FC is only minimally metabolized in the liver. Renal elimination is via glomerular filtration; no tubular resorption or secretion takes place. The half-life of 5-FC is c.3–4 h in patients with normal renal function, but can be extended up to 85 h in patients with severe renal insufficiency.19,23,25 Renal insufficiency alters 5-FC pharmacokinetics since it slows absorption, prolongs serum half-life and decreases clearance.22 The apparent volume of distribution of 5-FC approaches that of total body water and is not altered by renal failure.

Dosage must be adjusted in patients with renal impairment. Various recommendations have been made.22–25 Daneshmend & Warnock have suggested the following guidelines for the administration of 5-FC to patients with renal insufficiency.22 In patients with a creatinine clearance of >40 mL/min, a standard dose of 37.5 mg/kg every 6 h should be used. If the creatinine clearance is between 20 and 40 mL/min, the recommended dose is 37.5 mg/kg every 12 h. In patients with a creatinine clearance of <20 mL/minute, the dose of 5-FC should be 37.5 mg/kg once daily. Finally, if the creatinine clearance is <10 mL/min, frequent determinations of 5-FC concentration should be used as guidance for the frequency of dosing.

Clinical uses and trial results

5-FC monotherapy is effective in treating infections caused by C. neoformans, Candida spp. and T. glabrata, and in chromoblastomycosis and phaeohyphomycosis.19 However, the use of 5-FC as a single agent is limited, because of the prevalence of intrinsically resistant strains (about 10% of C. albicans isolates) and the frequent development of resistance during treatment. Monotherapy with 5-FC is now only used in some cases of chromoblastomycosis and in uncomplicated lower urinary tract candidiasis and vaginal candidosis.6 In all other cases, 5-FC is used together with other agents, usually amphotericin B, for the treatment of systemic mycoses.19,20

Cryptococcosis

The superiority of the combination of amphotericin B and 5-FC over either drug alone in cryptococcal meningitis has been described in case series,30 as well as in randomized trials.29,31–35 Bennett et al.34 found, in non-HIV-infected patients, that the combination of amphotericin B (0.3 mg/kg/day) and 5-FC (150 mg/kg/day) administered for 6 weeks was superior to amphotericin B alone (0.4 mg/kg/day) administered for 10 weeks. A similar trial evaluating the same combined regimen showed that treatment for 6 weeks
rather than 4 weeks was required for most patients. The authors suggested that 4 weeks' treatment may be used in non-immunocompromised patients with favourable prognostic signs, including a cerebrospinal fluid (CSF) cryptococcal antigen titre of <1:8 following treatment.

Several studies have been conducted in HIV-infected patients with cryptococcosis. In a retrospective study, the course and outcome of 89 eligible patients were reported. Forty-nine patients received a combination of 5-FC and amphotericin B, while 40 were treated with amphotericin B alone. There was a trend towards a higher survival rate in the group of patients treated with the combination. However, the relative efficacy of clearance of cryptococcal antigen from the CSF was not assessed and 5-FC concentrations were not monitored, so it is difficult to interpret the role of 5-FC. In a randomized study of a small population (42 patients, of whom 20 were eventually used in the study), the combination of amphotericin B and 5-FC was more effective than monotherapy with fluconazole. Recently, the results of a randomized, double-blind multicentre trial, in which patients with a first episode of HIV-associated cryptococcal meningitis were treated with high-dose amphotericin B (0.7 mg/kg/day) with or without 5-FC (100 mg/kg/day) for 2 weeks, were published. The combination of high-dose amphotericin B and 5-FC was associated with an increased rate of CSF sterilization and a decreased mortality 2 weeks after treatment.

In the treatment of cryptococcal meningitis, 5-FC may in the future be combined with ketoconazole, fluconazole or itraconazole, although currently these combinations are not satisfactory. Ketoconazole, amphotericin B, 5-FC and combinations of these drugs have been compared for chronic cryptococcal meningitis in steroid-treated rabbits. The combination of ketoconazole and amphotericin B was at least as effective as the combination of amphotericin B and 5-FC after a 2 week treatment regimen. In a mouse model of cryptococcal meningitis, the combination of 5-FC and fluconazole resulted in a significantly higher survival rate and a lower colony count of C. neoformans in brain tissue than either drug alone. However, such synergy between these two antifungal agents was not found in a study of experimental cryptococcal meningitis in rabbits. Recently, it has been shown that HIV-infected patients with cryptococcal meningitis might benefit from the combination of 5-FC and fluconazole. There have also been reports that show the superiority of a combination of amphotericin B and 5-FC over monotherapy with fluconazole. Furthermore, in a randomized study of AIDS patients with cryptococcal meningitis treated with either fluconazole or amphotericin B, it has been shown that fluconazole was as effective as amphotericin B. Itraconazole is less effective than the combination of amphotericin B and 5-FC in achieving a complete response in the initial therapy in AIDS patients with cryptococcal meningitis. A complete response was observed in five of 12 patients using itraconazole and in all 10 patients treated with amphotericin B and 5-FC. The combination of 5-FC and amphotericin B is also effective against large cryptococcal intracerebral masses (cryptococcomas).

Candidosis

Monotherapy with 5-FC in cases of systemic or disseminated candidosis has been shown to be effective in adults as well as in neonates and premature infants. However, resistance to 5-FC in Candida spp. is not rare and thus monotherapy of such infections with 5-FC is not recommended.

In vitro and in animal models, amphotericin B and 5-FC show synergic activity against a number of different Candida spp., so this combination is also used. Chronic infections such as candidal endophthalmitis and endocarditis can be treated with the combination of amphotericin B and 5-FC for long periods of time, in conjunction with surgery. The use of a combination of 5-FC and amphotericin B for the treatment of hepatosplenic candidosis has also been reported. Furthermore, it has been shown in a retrospective study that patients with candidal meningitis respond well to the combination of amphotericin B and 5-FC. 5-FC in combination with amphotericin B is beneficial in patients with candidal peritonitis associated with continuous ambulatory peritoneal dialysis, if the catheter cannot be removed. Finally, in the treatment of uncomplicated candidal cystitis, 5-FC has been used alone as well as in combination with amphotericin B. The role of 5-FC in the treatment of candidal urinary tract infections has been reviewed recently: the use of 5-FC for this indication is limited by the drug's toxicity and, perhaps, it should only be used under unusual circumstances or when azole-resistant organisms are involved.

It should be stressed that no randomized trials have been conducted to determine whether combination therapy with 5-FC and amphotericin B is superior to monotherapy with either amphotericin B or fluconazole for invasive candidal infections. Even so, combination therapy with amphotericin B and 5-FC is recommended for the following types of invasive candidosis: meningitis, hepatosplenic candidosis, endophthalmitis, endocarditis and peritonitis, especially those caused by C. tropicalis, Candida parapsilosis, C. krusei or Candida guilliermondii (which are inherently less susceptible to amphotericin B than C. albicans).

Future developments in the use of 5-FC in the treatment of candidosis lie in its combination with ketoconazole, fluconazole and itraconazole. 5-FC and itraconazole act synergistically in a murine candidosis model. Fluconazole and the combination of itraconazole and 5-FC have been shown to be equally effective, whereas fluconazole has been shown to be more effective than 5-FC alone for the treatment of oesophageal candidosis in HIV-infected patients. In surgical patients with deep-seated candida mycoses, the combination of amphotericin B and 5-FC eliminated the organism earlier than fluconazole alone.
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although the cure rates of the two patient groups were similar.57 In intensive care unit patients with pneumonia or sepsis due to Candida spp. and treated with fluconazole or with amphotericin B and 5-FC, no differences in clinical outcome were observed. However, the combination of amphotericin B and 5-FC was more effective than fluconazole for the treatment of patients with candida peritonitis and eradicated the infecting yeast better.58

Aspergillosis

5-FC is often added to amphotericin B in the treatment of invasive aspergillosis, primarily in cases of aspergillosis refractory to amphotericin B alone.53 However, there is no clear evidence that this combination is more effective than amphotericin B alone.53 Pulmonary aspergillosis has been effectively treated with 5-FC monotherapy. However, large comparative trials are lacking.

Chromoblastomycosis

The treatment of chromoblastomycosis caused by dematiaceous moulds has been hampered by the relative paucity of effective agents and particularly by the in vitro resistance of many of these moulds to amphotericin B.19 In a small series from the USA and a larger series from Brazil, 5-FC has been shown to be effective as monotherapy for chromoblastomycosis.53 Furthermore, there are case reports in which chromoblastomycosis has been cured with the combination of oral and topical 5-FC59 and with the combination of oral ketoconazole and 5-FC after monotherapy with ketoconazole had failed.60

Other mycoses

The combination of 5-FC and amphotericin B can also be used in the treatment of phaeohyphomycosis of the central nervous system, specifically caused by Xylohypha bantiana.45 5-FC is not effective in the treatment of blastomycosis, coccidioidomycosis, histoplasmosis or sporotrichosis.19

Cancer therapy

5-FC may have a new role in the treatment of different types of cancer, especially colorectal carcinoma. One of the new and promising therapeutic approaches that takes advantage of the effectiveness of 5-FU and minimizes its systemic toxicity is the use of an enzyme/prodrug combination in which 5-FC is combined with an Escherichia coli gene that encodes the enzyme cytosine deaminase.61 It is hoped that this combination will deliver high local concentrations of 5-FU at the tumour site. The topic of 5-FC and cancer therapy will not be explored further in this review.

Toxicity and drug interactions

5-FC is known to have some relatively minor side effects, such as nausea, vomiting and diarrhoea, it also has more severe side effects, including hepatotoxicity and bone-marrow depression.

Gastrointestinal side effects

Gastrointestinal side effects, the most common and least harmful side effects associated with 5-FC treatment, include nausea, diarrhoea and, occasionally, vomiting and diffuse abdominal pain. They occur in approximately 6% of patients treated with 5-FC.6 Although these side effects are usually not severe, two cases of ulcerative colitis and bowel perforation have been reported.6,53

Hepatotoxicity

Hepatotoxicity can occur during 5-FC treatment. In most cases it involves increases in serum concentrations of transaminases and alkaline phosphatase.7,28,30 The incidence of hepatotoxicity is not clear: most reports quote incidences of between 0 and 25%,7,29,62 although a recent study by our own group showed that hepatotoxicity could occur in up to 41% of patients.28 This apparent higher incidence of hepatotoxicity may have resulted from the definition of hepatotoxicity being stricter than that used in earlier studies, or increases in liver enzymes may not have been caused only by 5-FC, given the underlying illnesses in the patients investigated.

The increases in liver enzymes can usually be reversed if the dose of 5-FC is reduced and sometimes even when the dose is unchanged.14 Increases in the concentration of bilirubin in serum and swelling of the liver have also been reported rarely, but can be reversed by discontinuing 5-FC treatment.14 However, two cases of severe liver necrosis have occurred in patients who received 5-FC for treatment of candidal endocarditis.14

The mechanism of 5-FC’s hepatotoxicity is unknown, but it seems to be concentration-dependent, predictable, possibly avoidable with careful maintenance of peak 5-FC concentrations below 100 mg/L, and reversible with temporary discontinuation of the drug or a reduction in dose.19,62 Not all patients with high 5-FC concentrations will experience hepatotoxicity.19

Bone-marrow depression

The most severe toxicity associated with 5-FC treatment is bone-marrow depression. There have been several reports of serious or life-threatening leucocytopenia, thrombocytopenia and/or pancytopenia.63–65 In the study by Kauﬀman & Frame,63 four of 15 patients treated with 5-FC developed bone-marrow toxicity (leucocytopenia in three
and pancytopenia in one patient). All four patients had peak serum 5-FC concentrations of $\geq 125$ mg/L immediately preceding and during the initial period of bone-marrow depression, and 5-FC serum concentrations remained at $>125$ mg/L for 2–14 days in three patients. Although reduction in the serum concentrations of 5-FC resolved the bone-marrow depression in three patients, one patient died as a result of bone-marrow aplasia.

Several other studies have shown that 5-FC concentrations $>100$ mg/L are toxic. The largest study that examined 5-FC toxicity involved 194 patients who were also given amphotericin B. This study showed that bone-marrow depression (granulocytopenia and/or thrombocytopenia) occurred in 12 (60%) of 20 patients with 5-FC concentrations $>100$ mg/L, and in eight (12%) of 65 patients with 5-FC concentrations $<100$ mg/L. Bone-marrow depression became apparent in the first 2 weeks of therapy in 51% of these cases and during the first 4 weeks in 91% of these cases. Patients who have an underlying haematological disorder or who have undergone radiation treatment or myelosuppressive therapy are particularly likely to develop bone-marrow depression after 5-FC treatment.

Symptomatic HIV-infected patients may be more intolerant to 5-FC than patients without AIDS. A high incidence of bone-marrow depression has been described in these patients. However, other studies have failed to show any difference in the rate of adverse effects in HIV-infected and uninfected patients.

**Mechanism of toxicity**

The mechanism of toxicity of 5-FC is still not fully understood. It is likely that some of the side effects caused by 5-FC, for example hepatotoxicity and bone-marrow depression, are dose-dependent, although not all reports support this theory. Furthermore, it has been postulated that conversion of 5-FC to certain metabolites, especially 5-FU, could be one of the mechanisms of development of 5-FC-associated toxicity.

It has been shown that patients treated with 5-FC have detectable amounts of 5-FU in their urine and serum. 5-FU is known to cause bone-marrow depression and gastrointestinal complications, as seen with 5-FC therapy. In addition, it has been shown that 5-FU concentrations in patients treated with 5-FC are comparable to those in patients treated with 5-FC.

Diasio et al. found that 5-FU concentrations in the serum of two healthy volunteers during the 6 h after oral administration of 2 g of 5-FC ranged from 10 to 400 ng/mL. They also measured 5-FU concentrations in the serum of seven patients treated for cryptococcal meningitis with amphotericin B and 5-FC, of whom five had experienced haematological or other toxicity during 5-FC treatment. 5-FU concentrations ranged between 2 and 3060 ng/mL and in 20 of the 41 were $>1000$ ng/mL, a concentration that is in the range found after cancer chemotherapeutic doses and known to be associated with haematological toxicity. Moreover, it was found that the ratios of 5-FU concentration to 5-FC concentration varied from 0.11% to 3.45% and the ratio was $>1%$ in 21 of the samples analysed.

Harris et al. examined the capacity of the human intestinal microflora to convert 5-FC to 5-FU using an in vitro semicontinuous culture system that mimicked the intestinal microflora. The culture system was dosed with radio-labelled 5-FC initially and after 2 weeks’ chronic exposure to 5-FC (50 mg/day). No detectable production of 5-FU was observed up to 8 h after the acute dose. However, at 24 h and at all times for 4 days, increasing concentrations of 5-FU were detected. The authors concluded that enzyme(s) responsible for deamination of 5-FC to 5-FU can be induced in the intestinal microflora by chronic exposure to 5-FC and that this conversion may provide a mechanism by which 5-FC toxicity may occur.

The theory of conversion of 5-FC to 5-FU by the intestinal microflora was strengthened by a study in which the relationship between the gut flora status and the in vivo 5-FC conversion to 5-FU was investigated by fluorine-19 magnetic resonance spectroscopy analysis ($^{19}$F-NMR) of the urine of two patients treated with 5-FC and amphotericin B. Although 5-FU itself was not detectable in urine samples, there was a direct relationship between 5-FU metabolites and gut flora status. The authors stated that the fact that 5-FU was not detectable in the urine of the patients was a result of the fast degradation process of 5-FU occurring primarily in the liver and of the intrinsic insensitivity of the NMR method used.

In addition to the possibility of conversion of 5-FC to 5-FU by the human intestinal microflora, it has recently been shown that considerable amounts of 5-FU may be present in some 5-FC intravenous solutions as a result of both impurities in the raw material and the formation of 5-FU from 5-FC upon sterilization and storage.

**Monitoring toxicity**

It is widely believed that, during treatment with 5-FC, careful attention to drug dosage and 5-FC concentrations is important. Measurement of serum drug concentrations is necessary if high doses of 5-FC are being used or if prolonged therapy is required. Furthermore, dosage reduction and therapeutic drug monitoring (TDM) are required in patients with renal failure or those receiving nephrotoxic agents (such as amphotericin B), or experiencing haematological or gastrointestinal toxicity.

Currently, therapeutic drug monitoring of 5-FC is routinely performed in many institutions to assure effective 5-FC levels in the individual patient, to avoid resistance and to prevent serious dose-limiting toxicity. Usually, in patients treated intermittently with 5-FC, target trough and peak concentrations of 25–50 and 50–100 mg/L, respectively, are considered adequate. In patients treated with...
continuous 5-FC infusion, a serum concentration of 50 mg/L is recommended.

Drug interactions

The antifungal activity of 5-FC has been shown to be competitively inhibited by cytarabine (cytosine arabinoside) if co-administered to patients. Inhibition may result from 5-FC being taken up by susceptible cells by the same transport system. Therefore, therapy with cytarabine is a contraindication to the use of 5-FC.

Since the most harmful side effects of 5-FC (i.e. bone-marrow depression and hepatotoxicity) can be elicited by many other agents, it is necessary to be cautious when 5-FC has to be co-administered with drugs that could enhance these side effects, such as immunosuppressive or cytostatic agents. Furthermore, drugs that are known to be myelosuppressive, such as zidovudine, should be used with caution in patients receiving 5-FC. However, there is no evidence that concomitant administration of 5-FC with immunosuppressive or cytostatic agents produces synergy of bone-marrow depression or hepatotoxicity.

Concomitant administration of aluminium hydroxide or magnesium hydroxide suspension delays the absorption of 5-FC. However, this has only a small effect on total bioavailability.

Drugs that impair glomerular filtration will decrease the elimination of 5-FC and thus prolong the half-life of the drug. Probably the most important and most common drug interaction is the concomitant administration of 5-FC and amphotericin B in order to enhance the antifungal activity of both. How-
ever, amphotericin is highly nephrotoxic and concomitant use of 5-FC and amphotericin B will thus lead to an increase in 5-FC serum concentrations and 5-FC half-life.

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