The Clinical Pharmacology of Anastrozole

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Abstract

Anastrozole is a potent non-steroidal aromatase inhibitor that selectively inhibits aromatase. It is the first aromatase inhibitor approved by the US Food and Drug Administration as an adjuvant hormonal therapy in early-stage breast cancer. With most patients needing to take anastrozole for two to five years, it is important for physicians to understand the clinical pharmacology of anastrozole. Anastrozole has excellent oral bioavailability and is widely distributed throughout the body. It is extensively metabolised by the liver, with a half-life of 40–50 hours. Anastrozole is primarily excreted through the faecal route. Steady-state concentrations are achieved after seven days of once-daily administration. The standard dosage of anastrozole is 1mg/day orally. No dose adjustments are necessary based on hepatic or renal dysfunction. No significant drug–drug interaction has been reported with anastrozole use. This article is to summarise the existing knowledge of the pharmacokinetics of anastrozole.

Breast cancer is the most common cancer and the second most common cause of cancer death among women in the US.[1] It is estimated that two-thirds of the invasive breast cancers will be hormone-receptor-positive and will require long-term adjuvant hormonal therapy.

Reducing the effect of oestrogen is the main aim of hormonal therapy in treating hormone-receptor-positive breast cancer. The effect of oestrogen is reduced in two ways – by blocking the oestrogen receptor or by inhibiting oestrogen biosynthesis. The mechanism of action of aromatase inhibitors (AIs) is to inhibit oestrogen biosynthesis. AIs have established their role in treating metastatic hormone-receptor-positive breast cancer in post-menopausal women through a number of clinical trials.[2–5] In addition, multiple clinical trials have shown that AIs have superior efficacy compared with tamoxifen as an adjuvant hormonal therapy in post-menopausal women with hormone-receptor-positive breast cancer.[6–11] AIs are therefore the recommended first-line adjuvant hormonal therapy in post-menopausal women with hormone-receptor-positive breast cancer, either as monotherapy or as sequential therapy after tamoxifen.

The recommended duration of adjuvant AI therapy is usually two to five years. With the recommended treatment period being up to five years in the adjuvant setting, it is important for physicians to understand the clinical pharmacology of some of the commonly used AIs.

Aromatase Inhibitor Development

AIs have been around for over 20 years. Aminoglutethimide was the first AI in general clinical use. Its use was limited by its intermediate efficacy in inhibiting aromatisation and its low specificity, which resulted in significant side effects.[12,13] Roglethimide was the second glutethimide derivative, whose use was limited by its low potency and significant side effects.[14,15] The second-generation AI fadrozole was then developed and was found to be more specific than aminoglutethimide. It still has significant side effects as it suppresses aldosterone synthesis.[16,17] The third-generation AIs anastrozole, letrozole and exemestane have been developed most recently. They are superior in both their high oestrogen biosynthesis suppression and their specificity, resulting in very few side effects.[18] Among them, anastrozole and letrozole are non-steroidal AIs, whereas exemestane is steroidal. Anastrozole was the first third-generation AI to be tested in clinical trials in treating metastatic and early-stage hormone-receptor-positive breast cancer in post-menopausal women.

The advanced role of anastrozole compared with megestrol acetate in treating advanced breast carcinoma as second-line therapy after tamoxifen has been demonstrated in a number of clinical trials.[2,3] In addition, a randomised clinical trial comparing anastrozole with tamoxifen as first-line therapy for patients with advanced breast cancer demonstrated that anastrozole is significantly better than tamoxifen in prolonging time to disease progression.[5] Moreover, the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial reported an increased disease-free survival and time to recurrence with anastrozol (Arimidex) compared with tamoxifen. It also showed an improved toxicity profile in terms of the risk of endometrial cancer and thromboembolic events in women receiving anastrozole compared with tamoxifen.[19,20] As a result, anastrozole was the first AI approved by the US Food and Drug Administration (FDA) as an adjuvant hormonal therapy in early-stage breast cancer in 2002.[21] This article will focus on summarising the clinical pharmacology of anastrozole.

Clinical Pharmacology of Anastrozole

Mechanism of Action

Anastrozole is a potent non-steroidal AI, also called a type II AI. AIs are divided into two types based on the method by which aromatase is inhibited. Type I AI drugs are steroidal, and the only type I drug currently available is exemestane. Type I AIs bind irreversibly to aromatase and cause permanent inactivation. Type II AIs are non-steroidal. Anastrozole and letrozole are the currently available type II drugs. Type II AIs bind reversibly to aromatase by competing with the endogenous ligands for the active site of aromatase. They do this by forming a reversible bond to the haem iron atom in the active site.[22]

Standard Dose

The standard dose of anastrozole is 1mg/day – this dose recommendation resulted from two dose-finding studies conducted in healthy post-menopausal women.[23] In one study, volunteers took 3mg anastrozole daily for 10 days and in the other study volunteers took either 0.5 or 1mg anastrozole daily for 14 days. This was done to assess both the pharmacokinetics of anastrozole and the oestrogen-lowering effect of anastrozole. All three doses resulted in >80% reduction of oestradiol concentrations for up to 144 hours after the last dose of anastrozole. Further comparison of volunteers with oestradiol concentrations below the detection limit suggested that 1mg daily is required to achieve the maximal oestrogen suppression. In addition, serum concentrations of gonadotrophins or adrenal steroids were not affected by anastrozole administration.[23]

Another two studies comparing the effect of 1 versus 10mg/day anastrozole with megestrol acetate 40mg four times daily on post-menopausal women with advanced breast cancer showed that the 10mg dose of anastrozole did not result in greater clinical benefit.[24,25] As a result of these studies, anastrozole 1mg/day became the recommended therapeutic dose.

Pharmacokinetics

Animal studies with radio-labelled anastrozole have shown that anastrozole has good bioavailability when administered orally.[26] A human study later confirmed that it takes two to three hours after oral administration for anastrozole to reach maximal concentration.[23] Food intake does not significantly affect steady-state serum concentration of the drug.[22] Once absorbed, anastrozole is widely distributed throughout the body, with about 40% being bound to plasma proteins.[27] The pharmacokinetics of anastrozole is linear and does not change with repeated dosing.[28]

Anastrozole is extensively metabolised in the liver through N-dealkylation, hydroxylation and glucuronidation to produce three major metabolites, which account for 95% of the metabolites created.[27] Triazole is the major circulating metabolite of anastrozole and it is inactive.[28] The other two metabolites are a glucuronide conjugate of hydroxyanastrozole and a glucuronide of anastrozole itself. Anastrozole is primarily excreted through the faecal route. As hepatic metabolism accounts for 85% of anastrozole elimination, anastrozole pharmacokinetics have been studied in patients with liver cirrhosis resulting from alcohol abuse. Compared with subjects with normal hepatic function, the oral clearance of anastrozole in patients with stable liver cirrhosis was 30% lower. The plasma concentration of anastrozole was, however, in the same range as that observed in subjects with normal hepatic function. As a result, there is no dose adjustment required in patients with stable hepatic insufficiency.[28]

About 10% of the anastrozole dose is excreted unchanged in the urine. Sixty per cent is excreted as metabolites in the urine.[28] As a result, anastrozole pharmacokinetics do not change significantly in patients with renal impairment, as defined by creatinine clearance less than 30ml/minute/1.73m². Dose adjustment in patients with renal insufficiency is not necessary.[28]

Pharmacodynamics

Anastrozle is a highly selective AI as it significantly suppresses serum oestrogen metabolite (oestrone, oestradiol and oestrone sulphate) concentration without significantly affecting the concentrations of corticosteroids and other hormones, such as gonadotrophins or adrenal steroids.[23] Aromatase inhibition is primarily achieved by anastrozole as a prodrug. Anastrozole suppresses plasma oestrone (E_1) concentration by 81–87%, oestradiol (E_2) by 84–85% and oestrone sulphate (E_1S) by 94%.[29]

Drug–Drug Interactions

Anastrozole is extensively metabolised in the liver. However, the metabolic pathway has not been elucidated. *In vitro* studies demonstrated that anastrozole inhibited CYP1A2, CYP2C8/9 and CYP3A4 (with magnitudes in descending order) at concentrations unlikely to be achieved at therapeutic doses, but had no effect on CYP2A6 or CYP2D6.[30] Clinically significant drug–drug interactions are therefore unlikely but may occur if the patient is taking medicines that interact with the cytochrome P450 system.

The ATAC trial included a third arm of combined tamoxifen and anastrozole. This combination was not better than tamoxifen alone, but was inferior to anastrozole alone. A substudy of the ATAC trial showed that concurrent administration of anastrozole and tamoxifen lowered the concentration of anastrozole by 27% (90% confidence interval 20–33%; p<0.001). This was despite the fact that anastrozole suppression did not correlate with systemic oestradiol suppression.[31] In addition, the authors' group recently showed that simvastatin is unlikely to alter the pharmacokinetics of anastrozole in a clinically meaningful way.[32] It was found that 14-day treatment with simvastatin had no statistically significant effect on the plasma concentrations of anastrozole (median difference -4.2 [-22.1, 6.2]; p=0.36) and hydroxyanastrozole (median difference 0.03 [-0.08, 0.14]; p=0.73). Moreover, 14-day concomitant administration of simvastatin had no statistically significant effect on the plasma concentrations of oestradiol or oestrone sulphate (median difference 3.0 [-9.5, 19.0]; p=0.27).[32] A number of studies have investigated the drug–drug interactions between anastrozole and a few other drugs and showed little evidence of significant drug–drug interactions. In 2001, Yates et al. published a randomised, double-blind, placebo-controlled, single-centre trial on 16 healthy male volunteers who were randomised to receive either 11 days of anastrozole followed by placebo or placebo followed by anastrozole. All subjects received 25mg warfarin on day three of each treatment session. Comparing the pharmacokinetic data from both arms showed that anastrozole did not change the pharmacokinetics of warfarin. Nor did it change the pharmacodynamic feature of warfarin by affecting prothrombin time, thrombin time, activated partial thromboplastin time and factor VII.[33]

In 2003, Repetto et al. reported a 10-patient study evaluating the pharmacokinetic interaction between anastrozole and quinapril in elderly patients with breast cancer and hypertension. Patients were divided into two groups: one group treated with anastrozole for over 10 weeks and the other group treated with anastrozole for 10

weeks with concomitant quinapril being started four weeks after anastrozole. A pharmacokinetic study of the plasma concentration of anastrozole was performed on days 21, 28, 42, 56 and 70. The plasma anastrozole levels were compared between the two groups and showed no significant difference. In addition, hypertension was well controlled in all patients. There was no evidence of clinically significant drug–drug interaction between anastrozole and quinapril.[34]

In 2006, Carlini et al. reported a case of liver toxicity after treatment with gefitinib and anastrozole in a 63-year-old woman.[35] The study hypothesised the possibility of drug–drug interactions through CYP450, but concluded that this interaction was unlikely as the pharmacokinetics of gefitinib are not altered by CYP3A4 inhibitors.[36] In addition, this case report pointed out that in 2005 Polychronis et al. published a

randomised controlled trial comparing preoperative gefitinib versus gefitinib and anastrozole in treating 56 post-menopausal patients with oestrogen-receptor-positive, epidermal growth factor-receptor-positive breast cancer. Polychronis et al. reported that there was no effect of anastrozole on the pharmacokinetics of gefitinib, although data were not shown.[37]

Conclusion

Anastrozole is a potent non-steroidal AI that selectively inhibits aromatase. It is the first AI approved by the FDA as an adjuvant hormonal therapy in early-stage breast cancer. The standard dose of anastrozole is 1mg/day orally. There have been no significant drug–drug interactions between anastrozole and other drugs reported to date. ■

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