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# Use of MTX in the elderly and in patients with compromised renal function

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## ABSTRACT

*The absorption and distribution of MTX are unchanged in the elderly compared to younger RA patients, while both metabolism and renal/biliary excretion of MTX may be affected by age and should be considered when using this drug. Neither haemodialysis nor peritoneal dialysis effectively clears MTX, although high-flux dialysis may prove to be effective. The efficacy of MTX is equivalent in the young and elderly. The adverse event profile reveals a higher frequency of GI, lower and haematological toxicity in older patients, although the overall profile is not qualitatively different.*

Rheumatoid arthritis is a systemic inflammatory disorder that leads to synovial joint damage and destruction (1). The most commonly used disease-modifying anti-rheumatic drug (DMARD) is methotrexate, the efficacy of which has been proven in controlled trials (2). In patients with normal renal function the common dose of methotrexate has historically been 7.5 to 15mg/week, but in recent years a dosage of 25mg/week is often used (2). In previous chapters various aspects of methotrexate action were discussed. This chapter will concentrate on older patients and patients with renal insufficiency.

The elderly (>65 years old) are the fastest growing demographic population in the United States (3) and older patients ingest the most medications. As such, the manner by which medications affect us as we age is of interest. The effects of medications are influenced by a number of factors. These include pharmacokinetic factors, pharmacodynamic factors and external factors. All of these are intertwined. For example, absorption, distribution, metabolism, and elimination of drugs (pharmacokinetics) may change in older patients as a result of declining physiological function of several organs including declining renal

function (the result of arterial, arteriolar, capillary, and glomerular changes) and declining liver function or size (4-6). Additionally, external factors such as diet and polypharmacy may play a role in altered pharmacokinetics (7-10).

Pharmacodynamics may also affect drug efficacy in older patients, resulting from genetic factors and concurrent illnesses such as diabetes mellitus, hypertension, cardiovascular disease and age-related vascular degradation (7-11). Furthermore, the immune system of the elderly is altered, possibly resulting in a different spectrum of diseases in older patients (12, 13).

We will first describe physiologic changes with age as they affect pharmacokinetics and pharmacodynamics and their potential to affect drug efficacy and toxicity. We will then discuss methotrexate in those contexts, including the disposition of methotrexate in renal insufficiency, particularly as relative renal insufficiency is a normal state in older patients. Finally, we will briefly discuss the efficacy and toxicity of methotrexate in the elderly.

## Pharmacokinetics

### Absorption

The absorption of some drugs in patients over 60 years old can be affected by physiological changes such as the reduction in saliva production, lower gastrointestinal motility, reduced secretion of gastric acid and pepsin, and increased emptying time. Despite this, the majority of drugs are absorbed by passive diffusion in the gastrointestinal tract (GI) (14-16). Therefore, despite these changes, total absorption remains unaltered, probably because there is ample surface area for absorption in the GI tract.

### Distribution

The distribution of a drug can be affected by age-related decreases in cardiac

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output, circulation, and protein binding. With age, the vascular system loses its elasticity and compliance, impairing the function of many organs. Age-related vascular changes result from the thickening of the *tunica intima* and *media*, increasing wall stiffness (11). Furthermore, due to the diminished cardiac output and smaller stroke volume in the elderly, maximal oxygen consumption ( $VO_2\text{max}$ ) decreases at the rate of one percent per year after the age of 25 (17, 18). Additionally, distribution of water-soluble compounds may be delayed in the elderly due to diminished extracellular and intracellular water volume. Intravascular volume decreases by an average of 15% by the age of 80 and in the face of comorbidities such as heart failure, cirrhosis, and nephrotic syndrome, extracellular space can be even lower. At the same time, body fat increases by 18–36% by the age of 80. It is logical that distribution of fat-soluble compounds may be increased in older people (19, 20).

The binding of a drug to different plasma and tissue proteins can sometimes greatly affect its therapeutic effects, toxicity, and distribution (21). Proteins can act as drug carriers for transfer into the lipid layers of cells. More importantly, the plasma protein binding of drugs acts as a reservoir to enhance distribution to tissues. In the tissues the medications act at the cellular level, undergo metabolism and/or are eliminated (21). Acidic compounds (*e.g.* diazepam, phenytoin, warfarin, salicylic acid, and methotrexate) bind to human serum albumin (HSA), while basic compounds (*e.g.* lidocaine, propranolol) bind to  $\alpha$ -acid glycoprotein (22) and the concentrations of HSA and  $\alpha$ -acid glycoprotein can change with age or disease. Albumin concentration decreases by up to 20%, or around 0.5g/L, per decade (22). On the other hand,  $\alpha$ -acid glycoprotein concentration, while generally not affected by aging, tends to increase in people with acute illness or malnutrition. Despite changing concentrations of these important drug-carrying proteins, “free” drug concentrations are generally unaffected except transiently, as the fraction of unbound drugs does not change (23). If the binding capac-

ity of a drug to HSA is 95% and the remaining 5% is unbound, a drop or increase in HSA concentration will still result in the same 95% of the drug being bound and 5% being unbound. Age-related changes in albumin and  $\alpha$ -acid glycoprotein are *per se* therefore not usually clinically important. Instead, decreases in protein binding affinity, which can be associated with uremia, hepatitis, cirrhosis, nephrotic syndrome, epilepsy, and physical burns, can greatly affect protein binding affinity (23). On a theoretical basis, a decrease in affinity changes the fraction of “active” drugs and could lead to either greater effect or greater toxicity. A decrease in binding affinity and its consequent secondary pharmacodynamic effect would primarily influence drugs with high protein binding capacities such as gold sodium thiomalate (95%) or sulfasalazine (99%) (24), rather than drugs with low protein binding such as methotrexate (46%), sulfapyridine (50%), or 5-ASA (43%) (24, 25). Furthermore, elderly individuals who have any of the abovementioned health conditions may experience decreased drug-protein binding affinity.

Polypharmacy, too, can affect the availability of drug binding sites and increase drug efficacy or toxicity. One could speculate that drug-drug competition for protein binding could result in the displacement of a drug from an enzyme, leading to more unbound drug concentrations in tissues, which can lead to either increased effects or increased toxicity. A study performed by Hanlon *et al.* in 808 elderly patients concluded that adverse reactions in elderly patients depended in part on the number of medications taken (adjusted hazard ratio -1.07; confidence interval (CI)-95%; 1.05–1.10 per medication) (27). A study by Passarelli *et al.* in 186 elderly patients came to a similar conclusion (odd ratio: 1.10, CI-95%; 1.06–1.86 per medication) (28). With drugs with low-medium protein binding capacity this competition will not significantly affect drug action (26). In summary, drug distribution in elderly patients can be affected by the reduction in intracellular and extracellular fluid space (for water soluble

drugs) and by increases in total body fat (for lipophilic medications). The concentration of drug-binding proteins also changes with age but does not affect drug distribution because unbound drug fraction remains unchanged at steady state, independent of drug-binding protein concentration. Distribution of drugs with high protein binding capacity may be affected by decreases in protein binding affinity that may occur in association with comorbidities common in older patients. Polypharmacy, which is common in elderly patients, can also cause drug-drug competition for protein binding, affecting, principally, drugs with high protein binding.

### Metabolism

The liver is the most important organ involved in drug metabolism (29). Drugs are metabolised after extraction from the blood into the liver. A yearly 0.5–1.5% reduction in hepatic blood flow results in a cumulative 40% reduction in liver blood flow between the ages of 25 and 65 (14, 30–32). These changes result in slower clearance of drugs with high hepatic extraction ratios (blood flow limited metabolism) (19, 22) because the extraction efficiency of such drugs is highly dependent on blood flow rate (see Table I). On the other hand, the metabolism of drugs with low hepatic extraction ratios (capacity-limited metabolism) (19) is not affected by hepatic blood flow (see Table I).

The reduction in liver metabolism in the elderly can also be attributed to the 25–35% reduction in average liver size (4–6) and diminishing hepatic enzyme activity (34). In addition, the efficacy of drugs that are eliminated by the cytochrome enzyme system can be reduced due to aging (34). Phase I and II reactions in the liver are important for the metabolism of many substances, including drugs. In the elderly, greater impairment is seen in Phase I reactions (oxidation, reduction, hydrolysis, demethylation, and hydroxylation) (35, 36) of the p-450 cytochrome enzyme activity than in Phase II reactions. Phase II reactions are the most common pathway in drug inactivation and elimination. Thus, changes in hepatic

**Table I.** Drugs used for RA undergoing blood flow-limited *versus* capacity-limited hepatic metabolism (10, 33).

Flow-limited	Capacity-limited
Morphine Pethidine Amitryptiline Lignocaine	Salicylic acid Methotrexate

**Table II.** Drugs used for RA undergoing phase I *versus* phase II hepatic metabolism (10, 33).

Phase I	Phase II
Ibuprofen Lignocaine Imipramine Amitryptiline	Paracetamol Salicylic acid Morphine

metabolism do not often significantly impair drug metabolism in older patients (33). Within this particular realm (not accounting for other factors), dosage regimens in the elderly need to be adjusted only with those drugs that are metabolised by the Phase I cytochrome system (see Table II) (34).

Lastly, older patients lose liver size (4-6) and patients with cirrhosis and other severe liver diseases in which the total capacity of the liver is severely affected may not metabolise drugs adequately (37). Because pharmacokinetic changes affect liver metabolism and hepatic clearance of drugs (10), some drugs should be prescribed carefully to older people. In such cases, the prescribing physician should start with a low dosage of medication in elderly patients and increase only as needed.

In summary, the liver is the most important organ for drug metabolism. Changes in high extraction ratio drugs have been noted in older patients due to reduced hepatic blood flow. In addition, phase I reactions in the liver are reduced in elderly patients. The more common phase II reactions responsible for drug inactivation and elimination remain unchanged. Complicating these aspects of metabolism are changes in liver size, whether from aging per se or severe liver damage, and these changes can affect total drug metabolising capacity. These hepatic metabolism changes should be taken into consideration before prescribing drugs to elderly patients.

**Table III.** Summary: Pharmacokinetics in older people with RA.

Absorption	Does not change with age (14).
Distribution	Hydrophilic drug distribution can be affected by decreased intra-and extracellular fluid (19, 20, 22). Lipophilic drugs may be affected by increased fat (19, 20). Drug binding affinity may be affected by co-morbidities (23) Polypharmacy may displace highly protein bound drugs, leading to transient changes in distribution (27, 28).
Metabolism	Reduced due to reduced liver mass (4-6). Reduced for high-extraction ratio drugs which undergo blood flow-limited metabolism, and unaffected for low-extraction ratio drugs undergoing capacity-limited metabolism (25, 33, 6, 34).
Elimination	Reduced due to lower kidney mass, reduced renal blood flow, reduced glomerular filtration rates, and higher prevalence of glomerulosclerosis (9, 38-42). Longer half-life elimination rate often correlates to lower creatinine clearance in older people (43, 70, 72, 80).

*Elimination*

Elimination refers to the removal of a drug from the body. The organs responsible for the great majority of drug clearance are the kidneys, lungs, and gall bladder. In people aged 65 or above, changes in kidney physiology play a crucial role in the pharmacokinetics of drugs. About 15–30% of elderly patients have a glomerular filtration rate (GFR) of 30 to 60ml/min – similar to 3<sup>rd</sup> stage renal disease (38). For most people, renal function and glomerular filtration rate decrease by approximately 1ml/min per each year between the ages of 40 and 80. This is due to decreasing total renal mass, reduced nephron count (39), reduced mass of the renal cortex, reduced renal plasma flow, and decreased glomerular blood flow (19, 39-42). Studies based on autopsies of 80- and 39-year old individuals found the renal mass in the older subjects to be reduced by 32% while glomerulosclerosis increased from less than 5% at the age of 40 up to 30% at the age of 80 (9).

With these changes, adjustments in drug dosage regimens may be needed to prevent toxicity. Dosage adjustments are needed especially for water-soluble drugs in order to reduce drug accumulation in the body since 50–80% of such drugs are eliminated through glomerular filtration and only 9–26% (43-45) is eliminated through the biliary tract (46). When excreted through the biliary tract into the gastro-intestinal tract, drugs may be reabsorbed, thus entering an enterohepatic re-circulation. This is

true of a number of medications used in rheumatic diseases, including indomethacin and methotrexate (43, 45). Thus, drug dosage should be adjusted in the elderly if the elimination rate of the drug in question is highly dependent on renal function. In addition, because a reduction of cytochrome P450 activity was observed in patients with renal failure (50), liver disease must also be accounted in those with renal failure (47-49).

In conclusion, renal function plays a major role in drug pharmacokinetics. With age there is a reduction in kidney mass, renal blood flow, glomerular filtration rate, plus an increase in incidences of glomerulosclerosis. Water-soluble drugs should be prescribed carefully to patients with impaired renal function since most of the drug is eliminated through the kidneys with only a minor fraction eliminated through the bile.

*Pharmacodynamics*

Pharmacodynamics refers to the study of the effects of a drug on the body. With age there is an increase in the sensitivity of the body to drugs such as anticoagulants and cardiovascular and psychotropic drugs (22). An analysis of 127 drugs by Aymanns *et al.* concluded that there are age-related changes in drug pharmacodynamics and the common medication rule for older patients – ‘start low+go slow’ (38) is justified in most cases, except in life threatening circumstances. There are no data specifically addressing this possibility among the anti-rheumatic drugs.

### Immune system in the elderly

The immune systems of elderly patients are not as effective as those of younger patients. Thymic involution, a drop in the number of naïve T cells (12, 13), reduced cell-mediated immunity, and poor response to new antigens have all been documented in elderly patients (51). A study conducted using cytofluorimetric analysis of 129 healthy subjects aged between 18 and 105 concluded that the number of naïve T cells drops as people age. Younger subjects exhibited a naïve T-cell count of  $824 \pm 48$  cells/ $\mu$ L while the older group showed a count of  $177 \pm 28$  cells/ $\mu$ L. Interestingly, the CD8+ subset of naïve T-cells, while lower than the CD4+ subset in any age group, was almost completely lacking in the oldest subjects, with a mean count of  $13 \pm 4$  cells/ $\mu$ L (12). Alteration in the function of T Cells, especially antigen presenting cells (APCs), has also been noted in the elderly (12).

Based on the above data, elderly patients may have decreased ability to respond to neo-antigens and to process already recognised antigens.

### Methotrexate

Methotrexate was invented in the 1940s as a folic acid antagonist (52) and was initially used in cancer treatment. Today it is a commonly used DMARD (Disease-Modifying Antirheumatic Drug) and immunosuppressive agent (53). It is effective in doses between 5–25mg/week (54) and has been used extensively for RA treatment in patients of all ages, including the elderly (14).

### Pharmacokinetics of methotrexate

#### Mode of action

Methotrexate is classified as an anti-folate. It enters cells via the reduced folate carrier (RFC-1) and then becomes polyglutamated (55, 56). MTX and its polyglutamates prevent biosynthesis of *de novo* nucleotides through inhibition of dihydrofolate reductase (DHFR) (55–57). Because methotrexate inhibits the synthesis of purines and pyrimidines, it was used in the treatment of cancer. Polyglutamated metabolites of MTX also exhibit anti-inflammatory properties by inhibiting adenosine production through aminoimidazole-carboxamide ribonu-

cleotide tranformylase (AICAR) (52, 55, 58, 59). Adenosine has inhibitory effects on neutrophil function, phagocytosis, and the release of toxic metabolites. Furthermore, it regulates the activity of mast cells, lymphocytes, and monocytes (1, 59–61). Other anti-inflammatory effects of methotrexate arise from its inhibition of the production of IL-8 and effect on the chemotaxis of polymorphonuclear cells, thus decreasing their activation and migration through capillary membranes and decreasing prostaglandin production (62).

In summary, methotrexate is a folate antagonist at high doses and has anti-inflammatory effects at lower doses. It enters the cells via the folate carrier system and becomes polyglutamated. Polyglutamated metabolites of MTX have an inhibitory effect on adenosine synthesis which modulates the immune system and produces anti-inflammatory effects desired for RA treatment.

#### Absorption of MTX

The oral bioavailability of methotrexate is 67–70% but can vary greatly in individual patients, varying from 40% to 100% (54). Methotrexate administered orally is absorbed through passive diffusion in the gastrointestinal tract. Doses less than 30mg/m<sup>2</sup> are absorbed fully by passive diffusion in the GI tract while doses greater than 80mg/m<sup>2</sup> (not used in rheumatology) result in incomplete absorption (63). MTX absorption in the elderly is not different than that in the young (64). In addition, subcutaneous methotrexate dosing is being used very frequently. Its bioavailability is 13–27% higher than oral dosing (65, 66).

In summary, the absorption of MTX is independent of age and varies among patients; on average, 70% of methotrexate is absorbed. Subcutaneous dosing results in a somewhat higher bioavailability of the drug.

#### Distribution of MTX

Distribution of small doses of methotrexate in the body occurs with a half-life of 1 hour (1). Distribution generally occurs into extravascular tissue compartments such as the kidneys, liver, and synovium (2). Methotrexate is 35–50%

albumin bound so the decreases in albumin concentration in the elderly have minimal to no effects on MTX binding. For example, when the concentration of a competing drug such as salicylate increases twofold, the fraction of bound MTX decreases by only 10%, a clinically insignificant change for a compound with an albumin binding capacity of only 35–50% (*i.e.* 3.5–5% decrease). The primary metabolite of MTX, 7-OH-MTX, however, has a much higher binding capacity (95%) and is therefore affected more by competing compounds. However, the metabolite is only 10% as active as the parent compound, making the cumulative effect of the binding competition clinically insignificant (26). The concentration of a drug in a patient's bloodstream is dependent on the volume of distribution of the drug, which consists of the hydrophilic space for hydrophilic drugs and the lipophilic space for lipophilic drugs (19). Water-soluble drugs tend to have small volumes of distribution which might lead to increased drug-serum concentration in the elderly (22). Because methotrexate is a water-soluble (67) compound, its distribution may be affected in the elderly because they have less intracellular water (20). Diuretics may increase this effect (19). On the other hand, Mangoni *et al.* stated that the reduction in the volume of distribution of a drug is balanced by a decrease in renal clearance (22). Although specific data are lacking, the combination of low to moderate protein binding, water solubility and decreased renal clearance in the elderly make it unlikely that the overall distribution of MTX is significantly changed in this group of patients.

#### Metabolism of MTX

As with distribution, specific data on MTX metabolism in the elderly are missing. One factor that could potentially decrease MTX metabolism in the elderly is decreased liver mass (4–6). On the other hand, since MTX is a drug with a low extraction ratio (0.06) and undergoes capacity-limited metabolic clearance, it is not affected by variances in blood flow rate and is therefore unlikely to be affected by reduced hepatic blood flow in the elderly

(25, 33). In addition, polyglutamation, which occurs after MTX enters cells, is unlikely to change MTX efficacy and toxicity with age (at least there are no contradictory data regarding this issue). In contrast, the hydroxylation reaction that produces 7-OH-methotrexate via Phase I metabolism may be reduced in the elderly, which could potentially result in increased parent drug concentration, although no published data have supported this either. The various factors here make the prediction of the overall effect of age on MTX metabolism extremely difficult.

In conclusion, factors such as reduced liver mass and reduced phase I reactions can potentially affect MTX metabolism in elderly patients while decreased blood flow probably has little to no effect due to the low extraction ratio of MTX.

#### *MTX elimination in the general population and in RA patients*

Correlation between renal clearance of MTX and glomerular filtration rate (GFR) suggests tubular reabsorption of the drug, as renal MTX clearance is consistently lower than GFR. Concurrent drug metabolism is suggested because plasma clearance consistently exceeds renal clearance (68). The majority (50–80%) of MTX elimination occurs by way of renal tubular clearance. Another 9–26 % (43–46, 69) is eliminated through the bile, resulting in enterohepatic re-circulation.

The elimination half-life of MTX is usually 7.1 to 7.4 hours, although 17% of patients were found to have an extended elimination half-life of 26 hours. RA patients demonstrated an 80ml/min/m<sup>2</sup> MTX clearance (26, 43, 70). Low doses (7.5–15 mg/week) undergo biphasic or triphasic elimination. In a study involving 20 RA patients, 10mg/m<sup>2</sup> doses of IV MTX resulted in a mean terminal half-life of 10.5±6.4h (54). Another study conducted with 30mg/m<sup>2</sup> dosages of IV MTX observed a triphasic elimination with an initial half-life of 0.75±0.11h, a second half-life of 3.49±0.55h, and a terminal half-life of 26.99±4.44h (54). 7-OH-MTX, the principal metabolite of MTX, has a significantly prolonged half-life (54).

#### *MTX elimination in the elderly*

Since renal mass decreases in older people and glomerulosclerosis becomes more common with age, it has been suggested that older patients should be treated as if they had renal insufficiency (19). Methotrexate pharmacokinetic studies were conducted to compare the effects of the drug in older and younger RA patients. A study by Bressole *et al.* (1997), comparing RA patients in two different age groups (24–45 and 65–83 years), found that MTX unbound fraction and volume of distribution were similar between the two groups but the elimination half-life of free and total MTX was prolonged in the older group in comparison to the younger patients ( $p<0.001$ ). Unbound drug clearance in older patients was significantly lower than that in younger patients (169ml/min *versus* 225ml/min, constituting a 25% decrease. Total clearance figures corroborated this conclusion (95.9ml/min in the older group and 126ml/min in younger patients, constituting a 24% decrease) ( $p<0.001$ ) (71). Another study by Bressole *et al.* (1998) concluded that creatinine clearance correlated well with methotrexate clearance ( $r=0.60$ ) (72). These findings suggest that elderly people, who suffer from decreased creatinine clearance, should take MTX cautiously (perhaps starting at 75% of the usual dose, even with normal serum creatinines) to avoid potentially toxic plasma concentrations of the drug.

Since 9–26% of MTX is eliminated through the bile, Furst (1995) suggested that cholestyramine might be used to increase MTX elimination during renal failure or drug overdose; this suggestion has never been tested. Probenecid and salicylates can inhibit MTX clearance by impairing biliary and tubular renal secretion (26, 73–76). Bourke *et al.* found that monkeys pre-treated with very large doses of probenecid (700mg/m<sup>2</sup>) had 2.6 times lower total renal MTX excretion compared to non-probenecid-pretreatment (77). Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) also reduce overall MTX clearance, probably by interfering with tubular excretion (26, 78). In conclusion, renal insufficiency

due to decreased renal mass, creatinine clearance, and glomerulosclerosis can decrease drug elimination from the body. Because elderly patients more commonly experience these physiological changes, they should be closely monitored when they use methotrexate. While not contraindicating the use of methotrexate with drugs such as probenecid or NSAID, renal factors should be taken into consideration by physicians when prescribing MTX with these medications.

#### *Use of methotrexate in patients with renal insufficiency*

Elderly patients may be treated as people with renal insufficiency due to age-related decline in kidney function (14, 19, 72). Since MTX is cleared primarily via proximal tubule filtration, patients with renal insufficiency exhibit overall reduction in MTX clearance (79). Janknegt *et al.* showed that patients with severely impaired renal function displayed a mean renal MTX clearance of 2.8ml/min/m<sup>2</sup>, as opposed to 84.6ml/min/m<sup>2</sup> for patients with normal kidney function (43, 70).

In another study, 77 patients with renal insufficiency were administered 7.5–15mg of methotrexate intramuscularly. The subjects were subdivided into four groups based on creatinine clearance: less than 45ml/min, 45–60ml/min, 61–80 ml/min, and greater than 80ml/min. The results showed that there were significant differences in MTX concentration among the four groups in the 120 minutes following drug administration. The patients placed in group 1 (lowest creatinine clearance) had much higher drug concentrations than those in groups 3 ( $p=0.0036$ ) and 4 ( $p=0.00026$ ) (both groups had normal creatinine clearances). Similar differences were noted after 8 hours. Elimination half-life was also much longer in group 1 patients (mean 22.7 hours) than in the other groups, especially group 4 (mean 10.8 hours) (see Table IV). Thus, total MTX clearance was decreased by 39.8% in patients whose creatinine clearance was lower than 45 ml/min in comparison to the groups whose creatinine clearance was >60ml/min. These data also correlated

**Table IV.** Free and total MTX pharmacokinetics in RA patients.

Parameters	Group 1	Group 2	Group 3	Group 4
Total no. of patients	7	15	25	30
Age (y)	76.4	67.1	65.5	52.8
CL <sub>CR</sub> (ml/min)	39.8	55.8	68.1	103.5
Extent of unbound fraction (%)	54.1	59.8	58.5	57.4
Free MTX concentration (t=2h) (µM~)	0.34	0.28	0.25	0.24
Free MTX concentration (t=8h) (µM~)	0.11	0.074	0.075	0.064
Free MTX T <sub>1/2</sub> elimination (h)	22.7	13.7	12.0	11.5
Free MTX CL <sub>fu</sub> (ml/min)	118.5	162.8	171.1	206.0
Total MTX concentration (t=2h) (µM~)*	0.66	0.51	0.49	0.45
Total MTX concentration (t=8h) (µM~)**	0.21	0.13	0.12	0.11
Total MTX T <sub>1/2</sub> elimination (h)**	22.7	13.1	11.9	10.8
Total MTX CL <sub>fu</sub> (ml/min)	63.7	92.1	95.7	115.1
Vd (l/kg)	2.16	1.92	1.61	1.56

Creatinine Clearance= CL Group 1: CL<sub>CR</sub> <45ml/min; Group 2: CL<sub>CR</sub> =45-60ml/min; Group 3: CL<sub>CR</sub> = 61-80 ml/min; Group 4: CL<sub>CR</sub> >80. ~ 10 mg dose; \* p<0.01, \*\* p<0.001.

Modified from Bressole *et al.* (1998).

well with the subjects' creatinine clearance (r=0.60, p<0.0001) (72).

Because methotrexate is primarily eliminated through the kidneys, its dosage for individuals suffering from renal insufficiency should be adjusted to minimise toxicity (71).

One study analysed MTX efficacy and toxicity using aggregate data from 11 clinical trials involving 496 patients subdivided into two groups – those over 65 years old and treated with MTX for at least five years and those under 65. The older group of patients exhibited a similar rate of side effects to those in the younger group. However, patients with renal insufficiency had higher incidences of pulmonary and other toxicities than those who had creatinine clear-

ance of at least 99.8ml/min. Overall, the risk of severe toxicities quadrupled in patients with renal insufficiency (80).

In addition, Boey *et al.* recommends close monitoring of patients with stage 3–4 kidney diseases who are on low doses of methotrexate. He adds that others do not recommend prescribing methotrexate at all to patients with stage-5 kidney disease (2, 81-83).

When considering dialysis in patients using methotrexate or when considering using dialysis to clear methotrexate, it appears that peritoneal dialysis is ineffective, based on case reports (86, 87).

Regarding haemodialysis, Chatham *et al.* stated that taking MTX during ESRD may have deleterious effects (84). Janknegt *et al.* points out that di-

alysis is generally ineffective in helping clear the drug, as MTX has a low protein binding affinity (70). Case reports of three patients with end-stage renal disease (ESRD) taking MTX showed that usual haemodialysis was not helpful.

In contrast, haemodialysis with high flux dialysers can be used effectively to reduce high serum levels of methotrexate (85). A high flux dialyser (F-80) with high-flux membrane and large pore size was used in the study by Wall *et al.*; the study demonstrated significantly improved removal of methotrexate in patients with renal insufficiency. In another study of six patients, the mean plasma clearance of MTX during dialysis was 92.1±10.3ml/min. One patient with extremely severe renal dysfunction underwent seven dialysis treatments and displayed a mean 63% clearance of a high dose of MTX (7.2g/m<sup>2</sup>). Following daily haemodialysis, the drug was cleared completely in 5.6±0.3 days. It should be noted, of course, that dialysis cannot remove polyglutamated MTX which is sequestered within cells (70, 84).

The second organ responsible for clearance of MTX from the body is the gallbladder, which excretes up to 30% of the drug. Hepatic clearance of a drug into the bile is a compensatory pathway for drug elimination, especially in patients with renal impairment, and may increase to improve methotrexate clearance from the plasma in such patients (46, 26, 54). A study conducted by Nuernberg *et al.* examined a 64 year-old patient who underwent cholecystectomy. A tube was inserted into the bile duct, allowing complete monitoring of bile. This study showed that biliary elimination of both MTX (8.7–26.0%) and its principal 7-hydroxy metabolite (1.5–4.6%) was significant (46). Another study involving three patients showed that biliary MTX concentration was much higher than plasma concentration, confirming an enterohepatic circulation originating with biliary excretion of methotrexate (68). In conclusion, methotrexate elimination is highly dependent on renal function and is correlated with creatinine clearance. It should be prescribed cautiously in

**Table V.** Summary: Pharmacokinetics of Methotrexate in older people with RA.

Absorption	Does not change with age (14). Somewhat greater bioavailability when using subcutaneous MTX (65, 66).
Distribution	Volume of distribution of methotrexate (a water soluble drug) can change due to lower intra- and extracellular fluid (20, 22). Because MTX has low-to-medium protein binding, polypharmacy is less likely to affect its distribution (26).
Metabolism	Can be decreased due to loss of liver mass (4-6, 30, 34). MTX is a low extraction ratio drug (<0.06) and is not affected by decreased hepatic blood flow (25, 33). Hydroxylation reactions may be reduced due to a reduction in Phase I metabolism (35, 36).
Elimination	MTX renal clearance is prolonged due to reduced renal mass, reduced renal blood flow and/or glomerulosclerosis (19, 71). Low (<45 ml/min) creatinine clearance correlates with low MTX clearance (71). Some MTX elimination occurs through biliary excretion and enterohepatic re-circulation (43, 45). Polypharmacy, especially through interference with proximal tubular excretion ( <i>e.g.</i> probenecid, NSAID and aspirin) can affect MTX elimination (26, 73-76).

**Table VI.** Efficacy of MTX treatment in different age groups of RA patients.

	Group 1: <65 yr (n=416)			Group 2: >65 yr (n=53)			P*
	Baseline	Difference	P	Baseline	Difference	P	
Swollen joint count	7.6 ± 4.9	-3.7 ± 5.5	0.0001	7.7 ± 4.9	-3.2 ± 5.9	0.002	NS
Painful Joint count	8.6 ± 4.9	-4.9 ± 5.7	0.0001	8 ± 4.4	-3 ± 5.2	0.0006	NS
Morning stiffness (min)	99.4 ± 84.3	-60.1 ± 85.6	0.0001	113 ± 109.6	-60.2 ± 109.1	0.0002	NS
Ritchie Articular Index	13.4 ± 9.1	-7.2 ± 9.9	0.0001	12.9 ± 7.8	-5.3 ± 9.7	0.001	NS
Remission		37 (8.9)			7 (13.2)		NS
MTX weekly dose increase (mg)	9.9 ± 1.5	1.8 ± 3.5	0.0001	10 ± 1.7	1.6 ± 3.1	0.001	NS
Haemoglobin (g/dl)	12 ± 1.7	0.6 ± 1.6	0.0001	11. ± 1.8	1.1 ± 1.7	0.003	NS
Platelets (10 <sup>3</sup> /mm <sup>3</sup> )	342.7 ± 119.1	-47.1 ± 127.8	0.0001	337.5 ± 102.4	-71.2 ± 85.4	0.0004	NS
ESR (mm)	46.1 ± 30.2	-16.1 ± 28.2	0.0001	53.7 ± 27.2	-19.2 ± 25.5	0.0001	NS
CRP (g/l)	0.04 ± 0.09	-0.02 ± 0.096	0.06	0.04 ± 0.03	-0.02 ± 0.03	0.052	NS

ESR: erythrocyte sedimentation rate; CRP: C-reactive level.

P: p value for each of the group between baseline and the end of the study. P\*: p value between two groups.

Modified from Bologna *et al.* (1996).

patients whose creatinine clearance is <45ml/min and in those with 3<sup>rd</sup> and 4<sup>th</sup> stage kidney disease. When renal function declines, there may be greater enteric excretion. While neither peritoneal dialysis nor usual haemodialysis effectively remove methotrexate, high-flux dialysis appears to be an effective method for clearing methotrexate.

#### Efficacy of methotrexate

Methotrexate is considered by many rheumatologists as the basic cornerstone of RA therapy and there are ample data supporting its efficacy (1, 14, 19, 88-94).

Few data are available concerning the efficacy of MTX in older patients. Wolfe *et al.*'s observational study of 235 RA patients compared its effects on older (>65 years old) and younger (<65 years old) patients receiving treatment for an average of two years. The results suggested that older patients exhibited better methotrexate response as shown by greater improvement in their haemoglobin and erythrocyte sedimentation rate. This study concluded that methotrexate works at least as effectively in older patients as in younger patients (95). Another open prospective study by Bologna *et al.* analysed the efficacy of MTX in two different age groups over 8 years. Fifty-three RA patients aged over 65 and 416 patients less than 65 years old participated in the study. There was significant improvement in swollen and tender joints, morning stiffness, remission rates, global response and adverse

events as well as erythrocyte sedimentation rate, platelet volume, and haemoglobin in both groups; there were no significant differences between groups (see Table VI) (96).

In a retrospective chart review of 33 patients 60 years old and older, treated with 7.5mg MTX for a mean duration of 22 months, 70% of patients considered methotrexate to be effective in treating their RA. Unfortunately, there was no control group in this study (97).

In conclusion, MTX appears to be as effective in older patients as it is in younger patients.

#### Toxicity of methotrexate

Methotrexate accumulates in cells for prolonged periods (94, 98). In a 3.5-year study involving 40 RA patients conducted by Fathi *et al.*, it was found that MTX polyglutamates accumulated rapidly in the liver and were retained for prolonged periods at a steady state (35–56% of total MTX were polyglutamates at 1 year) (99). In rat livers, polyglutamates of MTX and 7-OH-MTX accounted for 54.7% of intracellular methotrexate 24 hours after drug administration (54) and these polyglutamates may be toxic (98). Animal studies have demonstrated that prolonged MTX circulation is associated with greater toxicity, especially in gastrointestinal cells and bone marrow (56).

Most patients tolerate methotrexate relatively well but 10–30% of patients stop taking the drug due to its toxicity (14, 76, 100). A 14-year study of

671 patients comparing anti-rheumatic drugs showed that methotrexate toxicity was the most common cause for discontinuation. Neither demographic factors nor disease duration, or disease severity significantly affected discontinuation of methotrexate (101).

The toxic effects of MTX on older people have not been extensively studied (14), but some data exist on methotrexate tolerability in the elderly.

One small open retrospective study examined the safety of methotrexate in elderly patients. Among 33 RA patients (32 female, and 1 male) aged >65 (mean age 78.8 years) who were treated with methotrexate for at least two years at a dose of 7.5 mg/week, there were no serious MTX-associated side effects. However, MTX was discontinued in four cases (12%); two patients ceased MTX because raised liver serum enzymes were noted and two stopped due to gastrointestinal adverse events. During two years of MTX treatment, haemoglobin increased from 12.4g/dl to 13.0 g/dl ( $r=0.226$ ,  $p<0.005$ ) and significant decreases within the normal; range were noted in the white cell count ( $7.9 \times 10^9/l$  to  $6.8 \times 10^9/l$  ( $r=0.184$ ,  $p<0.05$ )). The latter may reflect decreasing inflammation as the erythrocyte sedimentation rate also decreased (mean: 56.8 to 35.2mm/h ( $r=0.246$ ,  $p<0.01$ )). This study concluded that the treatment of elderly patients with MTX is moderately safe (102). A study of 469 patients conducted by Bologna *et al.* analysed the adverse events of MTX treatment on two different age

**Table VII.** Adverse effects from MTX treatment between different age groups.

	Group 1: <65 yr (n=401)	Group 2: >65 yr (n=51)
Gastrointestinal	82 (20.4)	5 (9.8)
Elevation of transaminases	50 (12.5)	6 (11.8)
Fatigue	15 (3.7)	1 (2)
Pulmonary	24 (6)	4 (7.8)
Cutaneous	10 (2.5)	0
Neurological	10 (2.5)	2 (4)
Haematological*	15 (3.7)	4 (7.8)
Miscellaneous	32 (8)	8 (15.7)

\*Thrombopenia, macrocytosis, and leucopenia. Numbers in parentheses represent percentages. Table was taken from Bologna *et al.* study (1996).

groups of RA patients (see Table VII). The results of the study did not show significant differences in adverse events between the two groups. Only haematological side effects such as macrocytosis, thrombocytopenia, and leucopenia were more common in the older group, resulting in a numerically (but not statistically) higher discontinuation rate ( $p < 0.07$ ). The credibility of the study results are somewhat marred by the fact that the dose of MTX was low (a mean of about 10mg MTX/wk) (96).

In addition, a study by Wolfe *et al.* concluded that toxic side effects varied little between two examined age groups (>65 years old and <65 years old) but gastrointestinal and pulmonary problems were seen more commonly in the elderly patients (95).

Hepatotoxicity and cirrhosis were noted in elderly patients with psoriatic RA taking methotrexate (95) and fibrotic changes in the livers of patients correlated with MTX dosage and duration of treatment. Although specifics were not mentioned, the prevalence of such diseases was significantly higher in older than in younger patients ( $p < 0.01$ ) (103). In summary, the adverse event profile of MTX in the elderly RA patient is different in detail from younger patients (e.g. numerically more frequent GI, liver and haematologic toxicity), but the overall toxicity incidence and severity is not qualitatively different from younger RA patients.

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