

When should I take my medicines?

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SUMMARY

Adherence to drug regimens is critical to optimise therapeutic outcomes. To aid adherence patient preferences must be discussed when considering the timing of doses, especially for chronic therapy.

The appropriate timing of administration should maximise therapeutic effects and minimise adverse reactions. If possible, doses should fit with the patient's daily routines.

Check if drug absorption is affected by meals. Food may increase or decrease absorption, and may also improve gastric tolerance.

Non-steroidal anti-inflammatory drugs are usually taken with food. For patients with acute pain, administration without food may be acceptable.

The best time to take antihypertensive drugs is uncertain. Chronotherapy studies may clarify any influence of evening or morning doses on clinical outcomes.

Introduction

Should the medicine be taken with or without food? What time is best to take my medicine – in the morning or at night? These are common questions posed by patients, especially when starting a new drug. For some drugs, incorrect timing may result in reduced efficacy (e.g. the progestogen-only pill) or poor tolerability. For others the significance of timing is unclear, for example do all statins need to be taken at night?

Appropriate administration should balance timing with patient preferences, especially for drugs used to treat chronic diseases for which adherence rates can be as low as 50%.¹ Strategies to optimise adherence include establishing the patient's preferences about the timing of doses, ensuring patients understand the importance of taking doses in relation to food, and simplifying the frequency of administration to once daily, for example using slow-release formulations, when possible.^{2,3}

With or without food?

Specific recommendations for dosing oral medicines in relation to food are available for approximately 40% of commonly prescribed drugs.⁴ Recommendations, along with practical advice, are included in most prescribing and dispensing systems, and in resources such as the Australian Medicines Handbook. There can be discrepancies in the advice given by different sources. This can be due to the approved product information not being updated when new clinical information becomes available.

Several factors influence drug administration in relation to food, including pharmacokinetics, efficacy

and, in particular, improving patient tolerance by minimising gastrointestinal upset (Table).

Pharmacokinetic food-effect studies assessing drug absorption are undertaken during drug development and inform the product information. Although food may alter the extent or rate of absorption through various mechanisms,^{5,6} not all pharmacokinetic effects are clinically relevant and some, such as flucloxacillin, are being reviewed.

Meal times can serve as a prompt for patients to remember to take their medicines, so instructions to take on an empty stomach may decrease adherence. If the desired therapeutic response is obtained, the question of taking a drug with food is less important. For example, levothyroxine is best absorbed on an empty stomach, however if adherence is of concern, it can be given consistently in relation to food⁷ and doses adjusted according to thyroid function tests. As a general rule, drugs for chronic diseases should be taken at consistent times relative to meals.

What time of day is best?

Information on the appropriate time of day to take medicines is often lacking. Only a limited number of drugs specify a time of day,⁴ but including explicit directions around timing on the labels applied at the pharmacy during dispensing is encouraged to help patients safely take their drugs.⁸ The timing of doses is important in some cases to avoid adverse effects, such as taking bisphosphonates in the morning once the patient is up and about to minimise the risk of oesophageal ulceration, and taking drugs with sedative effects at bedtime to minimise daytime

Table Taking medicines with or without food

Factors to consider	Clinically relevant examples
Absorption: Will absorption be impaired or enhanced if taken with food?	<ul style="list-style-type: none"> • If absorption is significantly impaired by food, give the drug at least 30 minutes before food, e.g. bisphosphonates such as alendronate, metronidazole benzoate (liquid)*, rifampicin. • If absorption is significantly increased with food, give the drug with or after a meal, e.g. griseofulvin, some antiretrovirals. • If absorption is impaired by food but tolerance is a concern, the drug can be given with food, e.g. erythromycin base*, roxithromycin, sodium fusidate.
Therapeutic effects: Will the drug be more effective if taken with or without food?	<ul style="list-style-type: none"> • Phosphate binders, e.g. calcium carbonate, must be taken with food to bind dietary phosphate in the gastrointestinal tract to decrease phosphate absorption. • Sulphonylureas are given with food to decrease the risk of hypoglycaemia.
Gastrointestinal factors: Will the drug be better tolerated if taken with or soon after food?	<ul style="list-style-type: none"> • To minimise gastrointestinal upset, including nausea and vomiting, give the drug with or soon after food, e.g. azathioprine, corticosteroids, erythromycin ethyl succinate, metformin, metronidazole*.

Compiled from the product information and the Australian Medicines Handbook.

* variable depending on salt

sedation. In general, appropriate timing must always be balanced with optimising adherence to treatment.

Diseases such as asthma and rheumatoid arthritis have circadian patterns in intensity and symptoms. Blood pressure displays a circadian variation by decreasing overnight.⁹ There is therefore renewed interest around the impact of circadian variation on dose timing.⁹⁻¹¹

Chronotherapy is the practice of altering the timing of doses in relation to individual circadian rhythms to improve efficacy and to minimise adverse effects.¹¹ This is important for corticosteroids, as cortisol release by the adrenal cortex follows a circadian rhythm.¹¹ Evidence for chronotherapy-based timing for other drugs is very limited, but is growing for antihypertensives and there is currently a large long-term study underway of nocturnal versus morning doses of antihypertensive drugs.¹²

Antibiotics

The appropriate dose and frequency of an antibiotic is determined clinically based on indication, severity of infection, and renal or hepatic function. Administration of antibiotics given more than once daily should be spaced as evenly as possible during waking hours. Examples of once-daily dosing include trimethoprim, taken at bedtime to maximise urinary concentrations overnight, and doxycycline, taken in the morning with food and a large glass of water or milk to reduce the risk of oesophageal ulcers.

Many antibiotics have recommendations regarding timing with meals. Of interest is ciprofloxacin which is approved to be taken irrespective of food, yet formation of non-absorbable complexes with metallic ions, such as

in calcium-rich food, has resulted in recommendations to take ciprofloxacin on an empty stomach.^{4,6}

A recent study¹³ reviewed pharmacokinetic data for flucloxacillin and found that food decreased total flucloxacillin concentrations. However, concentrations of free flucloxacillin that are associated with efficacy were obtained in most circumstances.

These results suggest that there could be flexibility with flucloxacillin administration, which may have significant implications for simplifying administration.

Antidepressants

Antidepressants with sedative potential are recommended to be taken at bedtime. Examples are mianserin, mirtazapine and tricyclic antidepressants, including low-dose amitriptyline commonly used for neuropathic pain. Antidepressants such as selective serotonin reuptake inhibitors which can cause insomnia are recommended to be taken in the morning. However, fluvoxamine and, to a lesser extent, paroxetine can cause somnolence and may need to be given in the evening.¹⁴ Some antidepressants such as duloxetine and venlafaxine are considered to have a minimal risk of sedation, so timing is guided by patient preference and tolerance.

Corticosteroids

Cortisol release by the adrenal cortex follows a circadian rhythm. Concentrations are higher in the morning and lower in the evening. Maintenance doses should therefore be given in the morning (with food) to mimic normal cortisol production and minimise adrenocortical suppression.⁹

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended to be taken with food to reduce the incidence of gastrointestinal adverse effects. There are no published studies proving that food modifies the gastric damage caused by NSAIDs,¹⁵ although patients anecdotally report improved tolerance with food. In acute pain, NSAIDs (especially ibuprofen) may be taken on an empty stomach to achieve higher plasma drug concentrations and an earlier analgesic effect. This may prevent patients taking unnecessary 'extra' doses of analgesia.¹⁶ The short-term use of over-the-counter NSAIDs appears to be safe with a low occurrence of severe ulcer complications, despite the uncertainty around the influence of food.¹⁶ Patients at high risk of NSAID-induced peptic ulcers may benefit more from prophylaxis, such as proton pump inhibitor therapy, rather than taking NSAIDs with food.¹⁷

Proton pump inhibitors

The appropriate timing of proton pump inhibitor therapy depends on the indication and patient preference. In gastro-oesophageal reflux disease, the drug should be taken half an hour before breakfast if symptoms primarily occur during the day, or half an hour before the evening meal if they occur at night.¹⁸ Taking the proton pump inhibitor before food may be beneficial when starting therapy or for intermittent use in symptomatic patients to ensure a high plasma concentration is available to bind to the active proton pumps.¹⁹ The timing with food or at specified times of day does not appear critical for other indications, as proton pump inhibitors achieve maximal acid suppression in two to three days.¹⁹

Statins

Statins lower cholesterol concentrations by inhibiting the enzyme 3-hydroxy 3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This follows a circadian rhythm and is principally produced between midnight and 6 am. Statins with a shorter half-life such as simvastatin and pravastatin are therefore recommended for evening dosing. Longer acting statins such as atorvastatin and rosuvastatin may be taken at any time.

A 2016 Cochrane review of chronotherapy-based dosing concluded that evening dosing of short-acting statins does not confer an additional benefit over morning dosing in terms of clinically relevant changes in lipids.²⁰ Patients should therefore take statins at a time that will optimise adherence. Further studies are needed to analyse whether chronotherapy affects clinical cardiovascular outcomes.

Antihypertensives

Blood pressure has a circadian variation. Patients whose blood pressure lowers during the night tend to experience fewer cardiovascular events compared to those whose blood pressure barely dips. This can be detected by 24-hour blood pressure monitoring. A hypothesis follows that nocturnal dosing of antihypertensives may be more cardioprotective than morning dosing.²¹

An early single-centre study of 2156 patients reported a reduction in cardiovascular events with nocturnal dosing of one or more antihypertensive drugs versus taking all antihypertensives in the morning.²² However this result was subject to criticism. A larger study in around 18,000 hypertensive patients also concluded that bedtime ingestion of one or more antihypertensives was associated with a significantly lower risk of cardiovascular morbidity and mortality.²³ The Treatment in Morning versus Evening (TIME) trial randomised 21,000 patients to take all their antihypertensive drugs either in the morning or evening. Its results are expected in late 2019.¹²

Whether the combined outcomes from these large chronotherapy studies will influence the timing of doses in international guidelines remains to be seen. In the interim, antihypertensive drugs may be taken consistently at a time of day that maximises adherence.

Diuretics are given in the morning, as diuresis at night may interfere with sleep and increases the risk of falls in older patients. If patients require twice-daily dosing, the diuretic potency determines the appropriate timing of the second dose. For potent loop diuretics, give the second dose at midday. For hydrochlorothiazide or amiloride, give the second dose before 6 pm.

Other resources

In addition to reviewing prescribing information and resources such as the Australian Medicines Handbook, consultation with a pharmacist or a medicines information centre may be helpful. They have access to specialised drug-interaction resources which can determine the clinical relevance of food on drug absorption and can source new research into the optimal timing of drug administration.

Conclusion

Encouraging patients to take their medicines to best fit in with their daily routine will optimise adherence. To further improve therapeutic outcomes, patients must understand the appropriate timing of doses

relative to food intake and time of day. To help patient-centred discussions, health professionals should regularly update their knowledge about the appropriate timing of administration. ◀

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