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Review Article

IMPORTANCE OF CLINICAL PHARMACOLOGY IN THE RATIONAL DRUG UTILIZATION (RDU) PROCESS

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Abstract

The concept of rational drug use during the past few years has been the theme of various national & international gatherings. Various studies conducted in developed as well as in developing countries during past few years regarding the safe & effective use of drugs show that irrational drug use is a global phenomenon & only few prescriptions justify rational use of drugs.

Keywords: - Clinical pharmacology, Disease development, ADR, Rational drug use

Introduction

The concept of rational drug use during the past few years has been the theme of variousnational & international gatherings. Various studies conducted in developed as well as in developing countries during past few years regarding the safe & effective use of drugs show that irrational drug use is a global phenomenon & only few prescriptions justify rational use of drugs. Clinical pharmacology is a medical discipline that links pharmacological and clinical expertise in order to promote rational use of drugs. The likelihood of a RDU program being accepted by the hospital medical staff, and becoming a tool for optimizing drug therapy will be greatly increased if members of the committee have adequate knowledge of clinical pharmacology. This is especially true when selecting or developing criteria.[1] This annex very briefly introduces various types of specialized knowledge that can enhance the effectiveness of a RDU program.

These types include:

- Disease etiology
- Dosage forms, and routes of administration
- Differences in drug requirements depending on severity of disease
- Drug-disease contraindications
- Adverse drug reactions
- Pharmacokinetics
- Combination therapy

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Disease etiology

When developing criteria it is necessary to consider and recognize the main pathogenic mechanisms of diseasedevelopment, since various mechanisms can be involved in producing the same manifestations. For example, thedevelopment of arterial hypertension may originate from fluid retention, increased cardiac output, or an increasein total peripheral vascular resistance. In each case, a different drug would be initially prescribed:

- A diuretic is the drug of choice for treatment of volume-dependent forms of arterial hypertension.
- In hemodynamic forms of arterial hypertension, beta-blockers, which decrease cardiac output, are considered to be the most effective.
- If the history of arterial hypertension development shows prevalence of total peripheral vascular resistance, vasodilators are indicated.

Rational prescribing of antibiotics depends on knowledge of penetration through the blood-brain, placenta, pleura,and peritoneum barriers; accumulation in organs, tissues and cells; the antimicrobial spectra; minimum inhibitoryconcentrations (MIC); and susceptibility of various microorganisms to antibiotics. For example:

- In patients with *Hemophilus*influenza meningitis, ceftriaxone concentration in cerebrospinal fluid is10,000 times higher than the MIC. For *Pneumococcal* meningitis, it is 1,000 times higher than the MIC.Therefore, this drug is a good choice for bacterial meningitis.
- Concentrations of cefaclor and cefuroxime axetil in sputum are 25-50 times higher than MIC for the majority of respiratory pathogenic organisms (*H.*

influenza, M. catharrhalis, Pneumococci), which determines the high clinical effectiveness of these drugs (up to 90%), and eradication of pathogenic organism from bronchi and lungs.

After administration of a 500 mg dose of ciprofloxacin, drug concentration in urine in patients withpyelonephritis reaches 400 mcg/ml, greatly exceeding the MIC for the main pathogenic microorganismsthat cause urinary tract infections (*E. Coli, Proteus, Pseudomonas aeruginosa*). This explains the higheffectiveness of ciprofloxacin and other fluoroquinolones in urogenital infections.

Dosage forms and routes of administration

Some drug use criteria often include dosage forms and routes of administration. Many drugs are available inseveral dosage forms with different biotherapeutic characteristics. For example:

- Knowledge of the fact that an oral or sublingual dose of nifedipine produces high plasma concentrations and a rapid response can be useful in treating hypertensive emergencies. The therapeutic effects of asublingual dose of nifedipine are comparable to an injection of clonidine. The oral route is safer than aninjection, and may be more applicable in outpatient or ambulatory settings.
- Special oral dosage forms are available that cause the active substance to be gradually released into theGI tract, achieving therapeutic plasma concentrations without reaching peak plasma concentrations, andtherefore avoiding "acute" side effects. Examples of drugs available in these extended release dosageforms are theophyllines and calcium antagonists such as verapamil, diltiazem, and nifedipine. Therefore,sustained release calcium antagonists are more acceptable for maintenance therapy of hypertension and prevention of angina.
- The severity of disease should be considered in development of drug use criteria, including the route ofadministration. In severe conditions, such as sepsis, endocarditis, severe pneumonia, and acutecardiovascular failure, it may be necessary to use a parenteral route of administration in order to rapidlyachieve maximum or therapeutic plasma concentrations.

Differences in drug requirements depending on severity of disease

The severity of a condition is a factor in determining whether a patient requires mono or combination drugtherapy. Normally, it is preferable to prescribe only one drug to produce a therapeutic effect, and increase ordecrease the dosage to modify the dose-related effect. There are some exceptions, such as when the dose-relatedeffect is unclear or where increases in dose produce little change in therapeutic effect, but increase side effects(e.g., hydrochlorothiazide, antiarrhythmic agents, and psychotropic drugs).

Monotherapy is recommended when treating a moderate infection caused by a known pathogenic organism toavoid antibiotic-induced side effects. However, multiple antibiotics may be necessary in known or suspectedmixed infections.

The dose-related approach should be utilized so as to allow modification of therapy when a drug's effectivenessappears to be insufficient, but given in normal dose ranges. However, in serious conditions, and in conditionswhere multiple mechanisms, organs, and systems are involved in the pathological process, monotherapy, evenwith maximum doses, may be insufficient. In such cases, combination therapy may be appropriate and necessary although additive therapeutic and side effects must be carefully considered in dosing.

Drug-disease contraindications

Optimal drug therapy requires consideration of a patient's total medical condition. In patients with multiplediseases, the drug of choice for one condition may be absolutely contraindicated, or should be used with cautiondue to another preexisting condition. Pregnancy and breast-feeding will also influence selection of drugs.

- If a patient is newly diagnosed with arterial hypertension, and also suffers from bronchial obstructionsyndrome or has a risk of bradycardia development, adrenergic blockers, especially nonselective ones,would be contraindicated in the treatment of hypertension.
- In pregnancy, the potential for a drug to be embryo toxic, teratogenic or organotoxic in the fetus, aswell as cause adverse effects on blood circulation and uterine tone in the mother, should always beweighed against the benefits of using the drug.

Adverse drug reactions

Rational drug use requires consideration of adverse drug reactions, which are defined here as any unexpectedreaction to a drug. This definition distinguishes adverse drug reactions from side effects, which are drug reactionsthat could occur, since the incidence has been documented in the literature. Because adverse effects are addressedonly after they appear, they can contribute significantly to morbidity and mortality, as well as add to the overallcost of

health care.

According to WHO statistics, up to 10% of the total number of hospital admissions are due to drug-inducedadverse reactions. While it may not seem possible to prevent adverse reactions, many are actually caused byincorrectly prescribed drugs.

- For example, use of gentamicin for treatment of urinary tract infections in patients with serious renaldisease, such as pyelonephritis, diabetic nephropathy, or renal amyloidosis, is not always justified dueto the fact that this drug may cause further progression of nephropathy. In such cases it is reasonableto replace gentamicin with azolide antibiotics such as azithromycin.
- It is recommended to avoid the prescription of drugs that are actively metabolized in the liver ofpatients with severe hepatocellular failure. For example, ketoconazole, long-acting benzodiazepines,nitrofuranes, and sulfonamides can increase hepatocellular injury.

Pharmacokinetics

It is essential to know the pharmacokinetic properties for each drug in order to be able to make rational decisions.The main indicators of a drug's behavior in a human organism are data on the drug's plasma half-life (T ½),elimination metabolism, distribution, and concentrations in plasma and tissues. Knowledge of drug metabolismand elimination is very important, since it can help avoid severe side effects in some cases. These data shouldalways be considered when developing drug use criteria for DUR. For example:

- In elderly patients there is a senile involution of kidneys where the volume of glomerular filtration isreduced by one-third in comparison with younger patients. This fact leads to prolongation of drugaction and to a decrease in clearance for those drugs that are mainly eliminated through the kidneys.For example, it may be necessary to reduce the daily doses of the histamine H -blockers ranitidine and famotidine, and the antibiotics cefaclor and cefuroxime, as much as one-third to one-half of normaldaily doses.
- In patients with renal failure it is mandatory to adjust daily doses of drugs based on creatinineclearance in the kidneys. For example, in patients with severe chronic renal failure, the daily dose ofciprofloxacin, histamine H -blockers, and digoxin, may need to be reduced by up to 75% of normal doses.

Combination therapy

As discussed previously, a patient may have multiple medical problems requiring use of several drugs. Even inpatients with one disease or condition, in some cases the use of a single drug does not always produce the desiredtherapeutic effect, necessitating combination therapy.

For example, favorable additive therapeutic effects are seen when a $-adrenergic blocker and a thiazide diureticare used together.

Similarly, the antibacterial spectrum can be broadened by concurrent use of cephalosporin and amino glycosideantibiotics, with the exception of cephalothin, which has been associated with increased incidence ofnephrotoxicity.

In cases of multiple drug use physicians and pharmacists should be aware of significant drug-drug interactions.

As seen above, a given combination of drugs can have both positive (desired additive effects, synergism, etc.)and negative (antagonism, adverse effects, etc.) results because of pharmacodynamic and pharmacokineticprinciples. For example, a combination of drugs with similar mechanisms of action, such as hydrochlorothiazideand furosemide, can result in a desired additive effect of controlling hypertension. However, this combinationcould also lead to an increase in the number and severity of side effects, such as hypokalemia, glucose intolerance,and myocardial infarction.

Just as combinations of drugs with similar mechanisms of action can lead to additive therapeutic effects,combinations of drugs with similar side effects can increase the risk of side effects.Concurrent use of drugs withsimilar side effects should be done with extreme care. For example, patients with severe ventricular arrhythmiamay require use of procainamide and disopyramide, both of which can cause A-V block.

Below are more examples of drug-drug interactions:

- The potassium-sparing diuretic spironolactone may increase plasma concentration of digoxin and itselimination half-life, increasing the risk of arrhythmias.
- Cephalosporins and amino glycosides can have nephrotoxic effects when used with loop diuretics.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), especially indomethacin, used with furosemide orhydrochlorothiazide, can reduce diuretic effects, possibly due to inhibition of renal prostaglandinsynthesis.
- NSAIDs used with methotrexate can cause fatal methotrexate concentrations in plasma and tissues.
- Indomethacin decreases the hypotensive effect of

the "-adrenergic blocker prazosin, the ACE inhibitorcaptopril, and the vasodilator hydralazine.

- Theophylline use with erythromycin, cimetidine, propranolol, and allopurinol (dosage .600 mg), willinhibit theophylline hepatic clearance, resulting in an increase in plasma theophylline concentrations,and leading to side effects such as tachycardia, nausea, tremor, and confusion.

The success in therapy is very much stipulated by the physician's ability to recognize the main components ofan individual patient's disease, and in turn to select a drug correctly, to define a drug dose and dosage schedule,to foresee possible unfavorable side effects (including those induced by drug-drug interactions), and to considerthe cost of treatment.

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