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REVIEW ARTICLE

FACTORS DETERMINING POWER OF HEAL

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ABSTRACT

It is almost that patient vary widely in their beneficial responses to drug therapy which causes adverse reactions which is going to be a major public health problem. Many factors play a crucial role in occurrence of adverse reactions, some of these are patient related or drug related etc,,. Age for instance has a very critical impact on occurrence of adverse affects, alcohol intake also has an impact, and other factors like gender, race, pregnancy, breast feeding, kidney problem, liver function, drug dose and frequency. And some more are the following categories of differences among individuals are responsible for the variations in drug response: (i) individuals differ in pharmacokinetic handling of drugs attain varying plasma/target site concentration of the drug. This is more marked for drugs disposed by metabolism than for drugs excreted unchanged. (ii)Variations in number or state of receptors, coupling proteins or other components of response effectuation. A multitude of host and external factors influence drug response. They fall in two categories viz, genetic and nongenetic including all environmental, circumstantial and personal variables. Though individual variation cannot be totally accounted for by these factors, their understanding can guide the choice of appropriate drug and dose for an individual patient. So, the present study discuss about some of the factors and reasons that effect the drug response.

INTRODUCTION

Ancient Greeks believed that the drugs are both poisonous and as well as an medicine to cure a disease. “Drug” it is a therapeutic agent, any substance other than food, used in the prevention, diagnosis, alleviation, treatment or cure a disease in man or animals. It can be a natural or synthetic substance which may have the capacity to alter the physiological state of living organisms. However the drug response after intake varies from individual to individual. Drug therapy is based on four major processes namely the pharmaceutical process, pharmacokinetics, pharmacodynamics [Takahashi H,Clin Pharmacol Ther. 2000;68:541–55] , and the therapeutic process. Here, the pharmacodynamics refer to “*what drug does to the body?”*, Pharmacokinetics refer “*what body does to the drug?*”. The way a person responds to a drug is affected by many factors, including genetic makeup, age, body size, the use of other drugs and dietary supplements like medicinal herbs, the consumption of food, the presence of diseases, storage of the drug, and the development of resistance and tolerance. For example, a large person generally needs more of a drug when compared, a smaller person needs for the same effect. Whether people take a drug as instructed also effects their response to it. But the concept of an average dose can be like “one size fits all”. It may fit a range of people well enough, but it may fit almost no one perfectly. Another horrible factor is that the drugs in today society are only effective in 60% of population. For example, every year in USA alone 2million people experience adverse effects and more than a 100,000 die from those adverse reactions. Hence the objective of the present study is, to discuss about the factors that effect the drug response in individuals**.**

Factors influencing drug response

Each person responds to drug in a unique way. Your drug response is not only due to the amount of the drug which you intake by also it gets affected by traits that we inherited from your parents, your physiological conditions, environmental conditions etc,,.. Because of these variations we cannot be absolutely confident that a medicine is without at significant risk. Surprisly, the dose of an particular drug that is right for you, for others may prove to be too little to have an effect or too high, thus causing serious side effects.

The major elements that are involved in influencing the drug responses are summarized below:

Classification

Intrinsic factors

a) Age
b) Gender

c) Pathological states: Liver function, gastrointestinal function, kidney function
d) Genetics
e) Psychological factor

Physiological factors

a) Pregnancy
b) Lactation

Extrinsic factors

a) Smoking
b) Diet and environmental
c) Drug Tolerance
d) Drug Dependence

Intrinsic factors

Age

Children are certainly not small adults. Generally, children responses to drugs have much in common with the responses in adults and indeed in other mammals. It is counter-intuitive to think otherwise. Most basic cellular and physiological processes and receptors are common to all mammals, irrespective of age or stage of development. For example, Children have a loop of Henley and a distal collecting tubule just as adults do, and therefore it is not surprising that diuretics work on a child's kidney. The magnitude of the effect may be different but the basic response has more features in common than there are differences. Often, it is assumed that drug effects differ in children but in reality this perception often arises because the drugs have not been adequately studied in pediatric populations of different ages and with different diseases. There may also be difficulties in measuring small but significant effects because the outcome measures are more difficult to assess in children[2]. For example, a study of an may be missed using cruder techniques such antiasthmatic drug in adults might show a 10% benefit in peak expiratory flow rate. In children under 5 years old who cannot perform such objective measures, a 10% difference as symptom diaries. Finally, part of the reason for the perception that pharmacodynamics are different in children is because the pharmacokinetics may be different at different ages. As a result, the same dose kg^{-1}does not result in the same circulating concentration because the absorption/metabolism/clearance gets differ.

Gender

Physiologic differences between men and women affect drug medication dosages. For example, because renal clearance is slower in women, some renally-excreted medications, such as digoxin, may require a dosage adjustment. Pharmacodynamic differences in women include greater sensitivity to and enhanced effectiveness of beta blockers, opioids, selective serotonin reuptake inhibitors, and typical antipsychotics[3]. Additionally, women are 50 to 75 percent more likely than men to experience an adverse drug reaction. Because women are prone to torsades de pointes, medications known to prolong the QT interval should be used with caution. Women should receive lower dosages of digoxin and have lower serum concentration targets than men because of higher mortality rates**.**

Pathological States

Drug-Disease Interactions

Sometimes, drugs that are helpful in one disease are harmful in another disorder. For example, some beta-blockers taken for heart disease or high blood pressure can worsen asthma and make it hard for people with diabetes to tell when their blood sugar level is too low. These drug-disease interactions can occur in any age group but are common among older people, who tend to have more diseases. Drugs generally produce a mixture of either therapeutic or adverse effects. Some of the common adverse reactions are[4]:

1. Hypersensitivity or Allergy reactions can occur within minutes or weeks after drug administration. The drug will interact with Antibodies, releasing histamines and other substances that produce reactions that can range from mild rashes to fatal anaphylactic shock.
2. Hepatotoxicity: hepatitis, necrosis. These include Acetaminophen, Aspirin.
3. Gastrointestinal effects: Anorexia, nausea, diarrhea, ulcers, colitis.
4. Nephrotoxicity: Gentamicin and Ibuprofen.
5. Hematological effects: Coagulation, bleeding, bonemaarow disorders.
6. Teratogenicity and carcinogenicity.
7. Reduced renal function can effect the elimination of many drugs and affect the plasma protein binding of drugs.
8. Changes in thyroid function can affect many aspects of absorption excretion and metabolism.
9. Changes in blood flow can influence ADME and therefore will have the potential to alter the effect of the drug.

Genetics

Differences in genetic makeup among individuals affect what the body does to a drug and what the drug does to the body. The study of genetic differences in response of drugs is called as “Pharmacogenetics” Dodic M, Hantzis V, FASEB J. 2002;16:1017–26. Because of their genetic makeup, some people process drugs slowly. As a result, a drug may accommodate in the body, causing toxicity. Other people metabolize drugs so quickly that after they take a usual dose, drug levels in blood never become high enough for the drug to be effective. In most cases, how a person responds to medication is not based on single genetic variant. Instead medication response is usually based on specific combination of genetic variants in or near gene (halo type). There can be different combinations of variants of each gene.

There are two main groups of genes that are important when studying variations in drug responses. The first, are those influencing the pharmacokinetic properties of drugs such as drug metabolizing enzymes and drug transporters, which effect the drug. One example of gene- ABCB1gene which is associated with resistance to the effects of drugs such as Anti-epileptic agent phenytoin Palmer LJ, Silverman ES. The second type is those influencing pharmacodynamics properties of drugs, including drug targets such as enzymes, receptors and ion channels which determine the drug effect on the body. One example of gene- CYP2C19gene which encodes the metabolic ezyme cytochrome P450 which is used to treat peptic ulcers, and other gastric complaints.

Drug-Drug Interactions

Clinically significant drug interactions, which pose potential harm to the patients, may result from changes in pharmaceutical, pharmacokinetics, or pharmacodynamics properties. Drug-drug interactions can involve prescription or non-prescription drugs. The patient factors that increase the risk for drug interactions include being critically-ill, polypharmacy, hypoxemia metabolic disturbances and being elderly. Tom-Revzon C.Pediatr Rev2006;27:315-7.

TYPES: Drug-drug interactions involve Duplication, Opposition, and Alteration of what the body does to one or both drugs.

Duplication

When two drugs with the same effect are taken, their side effects may be intensified .Duplication may occur when people inadvertently take 2drugs that have the same active ingredient. For example, people may take a cold remedy and a sleep aid, both of which contain "diphenhydramine" or a cold remedy and a pain reliever, both of which contain Acetaminophen**.**

Opposition

When two drugs with opposing actions interact, there by reduce the effectiveness of one or both. For example, NSAID'S such as Ibuprofen, which are taken to relieve pain, may cause the body to retain salt or fluid.

Alteration

One drug may alter how the body absorbs distributes, metabolizes, or excretes another drug. For example acid blocking drugs, such as histamine-2 blockers and proton pump inhibitors, raise the pH of stomach and decrease absorption of some drugs such as ketoconozole, a drug for fungal infections**.**

Psychological Aspects

Attitudes and expectations play a major role in a patient's response to therapy and the willingness to take the medication as prescribed. Patients with diseases that have relatively rapid consequences if therapy is ignored, such as type 1 (insulin dependent) diabetes, usually have a good rate of compliance[8]. Patients with "silent" illnesses, such as hypertension, tend to be much less compliant with the treatment regimen. Another psychological consideration is the "placebo effect" and the "nocebo effect". It is well documented that a patient's positive expectations about treatment and the care *received can positively affect the outcome of therapy, a phenomenon known as the* ***placebo*** **effect** (Latin, **I will please**). Although more difficult to prove because of ethical considerations, it is also felt that negative expectations about the therapy and the care received can have a nocebo effect (Latin, **I will harm**), resulting in less than optimal outcomes of therapy. It is thought that the **nocebo effect** plays a major role in psychogenic illness, especially in stress-related problems, by worrying about it. Caregivers can help diminish the nocebo effect by having a positive mental attitude and emphasizing the positive aspects of therapy **placebo** is a drug dosage form, such as a tablet or capsule, that has no pharmacologic activity because the dosage form has no active ingredients. When taken, the patient may report a therapeutic response. This response can be beneficial in patients being treated for such illness as anxiety, because the patient tends to take fewer potentially habit-forming drugs. Placebos are frequently used in studies of new medicine compared with the inert placebo. The American Pain Society and the Agency for Health Care Policy and Research recommend the avoidance of deceitful use of placebos in pain management violates a patient's rights to the highest quality of care possible.

Physiological Changes

Pregnancy

The physiological changes of pregnancy have been shown to alter the disposition of some drugs. However, there are no data on the possible influence of pregnancy or its complications on drug effect. We have applied drug concentration-effect analysis to determine whether pregnancy influences the action of propranolol. Twelve women with pregnancy induced hypertension were studied during the third trimester and again 2-3 months post partum. On each occasion propranolol (10 mg) was given intravenously and measurements of heart rate, blood pressure and whole blood propranolol concentration were blood pressure or pretreatment heart rate and the slope of the concentration-effect relationship[9]. It conclude that pregnancy can significantly alter determined over the ensuing 8 h. Pregnancy did not alter propranolol disposition. Clearance was 0.63 +/- 0.18 and 0.71 +/- 0.24 liter h-1 kg-1, and volume of distribution at steady state was 4.02 +/- 2.98 and 3.07 +/- 1.58 liters/kg during and after pregnancy respectively. There was no fall in blood pressure over the period of the acute study. The reduction in heart rate (beats/min per mg of propronolol/ml) was greater during compared with after pregnancy: -0.61 +/- 0.23 and -0.39 +/- 0.19 respectively (F = 6.64; df 1.9; P less than 0.03). There was non-relationship between drug effect in the absence of any pharmacokinetic changes. These findings suggest that therapeutic ranges established in non-pregnant patients may not be applicable during pregnancy.

Lactation

Most of the drugs can cross the placenta and expose the developing embryo and fetus to their pharmacologic and teratogenic effects. So during pregnancy if possible it's good to avoid giving any drug. Most antibiotics are detected in milk for example tetracycline, concentration in breast milk are 70%of maternal serum concentration, present a risk of permanent tooth staining in infant. Drug passage across the placenta is dependent on: i) Lipid solubility ii) Degree of drug ionization Marshall JD, Clin Pharmacol Ther.1999; 66:66–75. [Pub Med. For example, Thiopental, drug used for caesarian section crosses the placenta almost immediately and can produce sedation or apnea in new born child. Drug use during lactation: Most of the drugs are detectable in breast milk. So it should be taken in low concentration. If must, timing should be 30-60minutes after nursing, 3-4hours before the next feed. This allows many drugs cleared from mother's womb. Mother's taking anticancer therapy should avoid breast-feeding.

Extrinsic Factors

Smoking

Many interactions between tobacco smoke and medications have been identified. Note that in most cases it is the tobacco smoke— not the nicotine—that causes these drug interactions. Tobacco smoke may interact with medications through pharmacokinetic (PK) or pharmacodynamic (PD) mechanisms.

PK interactions affect the absorption, distribution, metabolism, or elimination of other drugs, potentially causing an altered pharmacological response. The majority of PK interactions with smoking are result of induction of hepatic cytochrome P450 enzymes (primarily CYP1A2). PD interactions alter the expected response or actions of other drugs. The amount of tobacco smoking needed to have an effect has not been established and the assumption is that any smoker is susceptible to the same degree of interaction. Agertoft L, Pedersen S. N Engl J Med. 2000;343:1064–9.

Diet

Dietary which we intake may affect the disposition of drugs. Nutrients include food, beverages and dietary supplements. Consumption of these substances may alter the effect of the drug response.

Food: Like food, drugs taken by mouth also be absorbed through lining of stomach or small intestine.

- Absorption: Increased or decreased when food is in stomach. Generally absorption is decreased.
- Distribution: A previously bound drug is displaced and this increases the concentration of drug in blood and this leads to an increased effect.
- Metabolism: High protein diets are associated with increased drug metabolism and high carbohydrates diets are associated with decreased metabolism. Malnourished adults have a decreased metabolism.
- Excretion: High protein diet increases kidney function. Often these interactions can be avoided by taking the drug 1hour before or 2hours after eating Mackenzie C. J Allergy Clin Immunol. 1998;101:451–5

Alcohol

Alcohol consumption is one of the most common risk factors contributing to physical and psychological ill health ,death. Many people do not consider alcohol a nutrient, but it effects body processes and interacts with many drugs. For example, taking alcohol with the antibiotic metranidazole can cause flushing, headache, palpitations and nausea and vomiting Tom-Revzon C. Drug Interactions. Pediatr Rev2006;27:315-7.

Drug tolerance

Drug tolerance occurs when a person begins to require a higher dosage to produce the same effects that a lower dosage once provided. An example is the person who is addicted to heroin. After a few weeks of use, larger doses are required to provide the same "high". Tolerance can be caused by psychological dependence, or the body may metabolize a particular drug more rapidly than before, causing the affects of drug to diminish more rapidly Pearce S, Budge H, J.Endocrinol. 2005;184:351–9..

Drug dependence:

Drug dependence, also known as ***addiction*** *or* ***habituation***, occurs when a person is unable to control the ingestion of drugs. The dependence may be physical, in which the person develops withdrawal symptoms if the drug is withdrawn for certain period, or psychological, in which the patient is emotionally attached to the drug.

Drug dependence occurs most commonly with the use of the schedule, or controlled, medications such as opiates and benzodiazepines. Many people, especially elderly, worry about becoming addicted to pain medication and therefore may not take pain medication even when it is needed. The nurse needs to assure them that studies have shown the less than 1% of patients using opioids for pain relief become addicted, and that it is important for their overall well-being to be as pain-free as possible.Kongkaew C *et al*, 2008

CONCLUSION

Many factors affect the occurrence of adverse drug responses (ADR's), some of these factors can be changed like smoking, or alcohol in-take others cannot be changed like age, presence of other diseases or genetic factors. Understanding the different affects if these factors on ADR's enables health care professionals to choose the most appropriate medication for that particular patients it also helps the health care professionals to give best advice to patients. Pharmacogenetics is the most recent science which emphasizes the genetic predisposition of ADR's. The innovative science provides a new perceptive in dealing with the decision making process of drug selection.

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