For a treating physician, the accurate knowledge of the pharmacokinetics of a drug aids in drug prescribing. The pharmacokinetic parameter of plasma half life (t½) is essential in deciding the dosing schedule and frequency of administration of a drug which in turn decides the compliance of the patient. Thus, it is essential for a physician to be fully aware of the dose-response and t½ relationship. However, in case of some drugs the t½ knowledge may not be helpful in deciding the dosage schedule or frequency of drug administration due to their ‘hit and run’ effect. Like the pharmacokinetic aspects, the pharmacodynamics of the drug also plays an essential role in deciding the drug of choice for the specific condition. Some mechanisms of drugs affix a new pharmacodynamic action to the drug (e.g. antiplatelet action of aspirin which initially was only an analgesic) which makes the drug uniquely different from the rest of the compounds in its category. A few of drugs with such different facets of action present their unique properties owing to the ‘hit and run’ effect. This short review focuses on discussing the drugs possessing this type of a pharmacokinetic and dynamic picture due to the ‘hit and run’ effect and the clinical utility of such drugs.

KEY WORDS: Dose response relationship, ‘Hit and run’ drugs, Plasma half life

INTRODUCTION

As is known, plasma half life (t½) of a drug is defined as the time required for body to eliminate or biotransform half of the amount of the drug present in the body at any given point of time [1]. Almost five t½’s are required to eliminate 97% of the drug out of the body. In general, drugs with short t½’s are given by i.v. infusions e.g. dopamine, while some other drugs with shorter t½’s are given at intervals longer than 5 times their t½ either because the continued presence of the drug is not required or the effect outlasts the plasma concentration [1].

The drugs whose effects or efficacy or actions outlast their plasma concentration form a very significant group and have led to the introduction of the term ‘efficacy half-life’. This is defined as time for a drug to lose half its effectiveness or efficacy. Obviously, this is difficult to determine and less precise than a plasma concentration of a drug, nonetheless the concept is valid [2].
At times, it is noticed that a drug with a relatively short $t_{1/2}$ is still able to produce the effect long after it has been eliminated, due to its intracellular action and its partial binding to the receptor long after most of the extracellular drug has been eliminated due to a phenomenon called the ‘hit and run’ effect [1,2]. These agents who initiate a cascade of events that continue after the drug has left circulation are known as ‘hit and run’ drugs [2,3,4]. Thus, the knowledge of the relation between the dose, blood level and the effect is not of much clinical importance in case of ‘hit and run’ drugs. However, the knowledge of the peak concentration is very useful as the pharmacodynamic effects of such drugs may only be related to their peak plasma concentration [5]. Also, the peak plasma concentration is related to adverse drug reactions due to these drugs [6].

In this connection, the exposure-response document focuses on human trials with the understanding that exposure-response information in animal/toxicological studies is also useful in integrating drug development and regulatory review processes. This information about the drugs helps in correlating the pharmacokinetic / pharmacodynamic responses of the drugs [6]. Measuring the pharmacokinetic parameters like $t_{1/2}$ and peak concentration is usually very beneficial in drugs with low safety margin, those with large inter individual variations, toxic drugs, poisonings, failure of response without apparent reason and to check patient compliance.

However, the measuring of plasma concentration i.e. therapeutic drug monitoring (TDM) is of no value in relation to the ‘hit and run’ drugs, whose effect lasts much longer than the drug itself [7]. The drugs which are known to produce these ‘hit and run’ effects are viz. Reserpine [2,7], Guanethidine[7], Omeprazole[7,9], Monoamine Oxidase Inhibitors (MAOIs)[2,7], Atypical Antipsychotics[9], Antineoplastic drugs,[2,10] Cortisone[3], Desmopressin (DDVAP)[11], Aspirin[3], Cocaine[12], Methylldopa[13], Prostacyclin[14], Penicillins[15] and Aminoglycosides [16]. Table 1: ‘Hit and run’ drugs with their mechanism of action, $t_{1/2}$, duration of action and uses have been mentioned. The implications of the ‘hit and run’ phenomenon are also responsible for some of the pharmacodynamic characteristics of the drug which will be discussed in this brief review of ‘hit and run’ drugs.

**Reserpine**

Reserpine derived from the roots of *Rauwolfia Serpentina* was isolated in 1955 and was found to act by causing catecholamine (CA) and serotonin (5-HT) depletion.[7] It causes a long lasting impairment of the storage mechanism for noradrenaline (NA), dopamine (DA) and serotonin (5-HT), and irreversibly inhibits the active amine transporters, thus the monoamines are gradually degraded and depleted by monoamine oxidase (MAO). The effect of reserpine lasts long after the drug is eliminated which is thus the ‘hit and run’ effect of the drug [7,8]. Reserpine that is bound to isolated storage vesicles cannot be removed by dialysis, indicating that the binding is not in equilibrium with the surrounding medium. Because of the irreversible nature of reserpine binding, the amount of drug in plasma is unlikely to bear any consistent relationship to drug concentration at the site of action [17]. Higher doses deplete CAs and 5-HT in the brain as well causing sedation and mental depression. Antipsychotic effect (mild) and extra pyramidal symptoms are produced due to DA depletion [7]. Low dose of reserpine combined with diuretics is used in the treatment of hypertension, especially in the elderly but now obsolete [17].

**Omeprazole**

Omeprazole is a proton pump inhibitor which inhibits $\text{H}^+\text{K}^+$-ATPase enzyme and terminates gastric acid production. The acid production resumes when adequate quantity of new enzymes are synthesized which takes several days. As a result acid-blocking action disappears, not because the drug disappears, but because new enzyme appear. The process of enzyme synthesis occurs with its own dynamics, without the influence of the drug. The resulting pharmacodynamics of omeprazole characterized as ‘fast onset/slow offset’, in that the drug’s blockade of acid secretion take place in an hour or so of dose administration, but then continues for 2-3 days without re-medication and thus omeprazole shows ‘hit and run’ effect [8].
Omeprazole is used to promote healing of gastric and duodenal ulcers and to treat Gastroesophageal reflux disease (GERD), including erosive esophagitis. It is the mainstay in the treatment of Zollinger-Ellison syndrome and is approved for the self-treatment of heartburn. Some drugs acting by irreversibly inhibiting enzymes also exhibit ‘hit and run’ effect like aspirin. Termination of these effects relies on synthesis of new platelets, so that there is no relationship between drug concentration and effect [18]. Aspirin seems to be an exception to most other COX inhibitors as it mediates analgesic effects by its major breakdown product salicylic acid, a weak inhibitor of PGE2 production [19].

However, aspirin initiates a ‘hit and run’ effect on COX-1 in platelets, where the enzyme is permanently acetylated and not replaced, owing to a lack of de novo protein synthesis in platelets [20]. Hence, although aspirin exemplifies both analgesic and ‘hit and run’ effects, the pharmacokinetic characteristic of this drug defines the analgesic effect [3]. Aspirin decreases the incidence of transient ischemic attacks, unstable angina, coronary artery thrombosis with myocardial infarction and thrombosis after coronary artery bypass grafting [21]. Aspirin’s main adverse effects at antithrombotic doses are gastric upset (intolerance) and gastric and duodenal ulcers [21]. The mechanistic features of ‘hit and run’ effect of aspirin is also showed by Clopidogrel which permanently inactivates the platelet ADP receptor P2Y12 through short lived active metabolite [18].

Desmopressin
Desmopressin (DDAVP, 1-deamino-8-D-arginine vasopressin), a synthetic vasopressin derivative has been used in patients with bleeding after cardiac surgery to reduce postoperative blood loss and transfusion requirements. DDAVP structurally differs from the natural hormone by deamination of homocystein at position 1 on the molecule, and substitution of D-arginine for L-arginine at position 8. This gives DDAVP both greater potency and a more prolonged duration of antidiuretic effect and markedly decreased pressor activity compared to vasopressin [22]. DDAVP was used for the first time in 1977 to treat patients with haemophilia A and von Willebrand disease (vWD) the most frequent congenital bleeding disorders [23], following the observation that DDAVP increased circulating factor VIII and von Willebrand factor (vWF) in healthy individuals [11]. The terminal half-life of DDAVP in plasma is about 4-5 hours, irrespective of the mode of administration. As the effect is of the ‘hit and run’ type, the DDAVP disappearance curve is probably of minor importance for the haemostatic effects, it is however, more important for the duration of antidiuretic effect, which is considered as a side effect when the drug is used for haemostatic indications [11,22]. In some cases therefore, the ‘hit and run’ effect which retains the action of the drug longer is considered as a side effect as in the case with DDAVP.

Atypical Antipsychotics
Atypical antipsychotics are newer (second generation) drugs discovered in 1951. They have weak dopamine D2 receptor and potent 5-HT2 blocking activity. They shows ‘hit and run’ mechanism by not consistently binding to receptors but positioning themselves to remain on the receptor long enough to exert therapeutic effect and dissociating before causing extra pyramidal symptoms or worsening of negative symptoms [7,9]. Their major limitation is higher incidence of agranulocytosis and blood dyscrasias. Other side effects include sedation, unstable BP, tachycardia, urinary incontinence, weight gain and precipitation of diabetes [7]. They are used in the treatment of schizophrenia, bipolar depression, and major depression with psychotic disorders/without psychotic features. They are used in the treatment of resistant major depression along with selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitor (SNRIs) [24].

Monoamine oxidase (MAO) inhibitors
MAOIs are the other group of drugs which irreversibly block the enzyme MAO and produce a ‘hit and run’ effect [18]. These drugs used as antidepressants have a long lasting action because the resynthesis of MAO after enzyme inhibition takes longer to recover. Given in small daily doses these MAOIs inactivate little of the enzyme each day. In this way the inhibition of the enzyme gradually increases even though the drug concentration in the tissues does not. Finally when
most of the enzyme is blocked the CAs and 5-HT accumulate in the body and exert their actions [25].

Selegiline is a MAO-B selective inhibitor. The complexity of the pharmacological activity of selegiline cannot be considered only as a result of a simple MAO-B inhibition. The mechanism of its action along with those of its metabolites was studied for neuroprotective action against the noradrenergic neurotoxin DSP-4. The results suggested that the uptake inhibitory effect of selegiline, and mainly that of its metabolite (-)-methylamphetamine (MA), played an essential role in the protection. MA was more potent to inhibit the uptake of NA and DA, than the parent compound. Neither selegiline nor its metabolite inhibited the reuptake of 5-HT. The results of this study state that MAO-B inhibition, which is due to the parent compound, is an irreversible ‘hit and run’ effect, the level of which after an initial phase is independent of the presence of the substance which caused it and the uptake inhibition is a reversible process and strictly proportional to the concentration of the substance responsible for the effect. In this regard the uptake inhibitory action of the metabolites exceeds that of the parent compounds. The role of the reversible uptake inhibition in neuroprotection may partly explain the need of the daily administration of selegiline to parkinsonian patients in spite of the irreversible MAO-B inhibitory action of the drug [26].

Cocaine

In some of drugs the ‘hit and run’ effect is responsible for the characteristic euphoric effect/ “kick” as in case of cocaine. Cocaine has a relatively short half life in the plasma and in the brain. When administered i.v. to humans, the half-life is in the range of 16 to 87 min (18 to 30 min in rats). This short life accounts for the rapid euphorogenic effects of the drug. Typically, when the drug is administered i.v., it produces a fast ‘hit and run’ effect by potentiating the extracellular levels of DA. When rats are given a continuous flow of DA i.v., they experience a peak in DA levels in 10 minutes, followed by a return to regular levels after 20 to 30 minutes. Because the initial high experienced by cocaine abusers lasts for only a short time, the initial stimulatory actions of cocaine can be attributed to the elevation of synaptic DA levels and hence the ‘hit and run’ effect [12].

Methyldopa

‘Hit and run’ effect though be responsible for an extended response of the drug in the body but in some cases the mechanism involved may be unclear as in case of methyldopa. There exists a considerable individual variation in the percentage of methyldopa absorbed from the intestinal tract which probably accounts in part for the widely varying doses required to obtain a therapeutic response in different patients. In any given patient, however, it is generally true that the blood pressure response is a relatively smooth one on a 6 or even 8 hour schedule of dosage of methyl dopa. In view of the rapid disappearance of drug from the plasma and its quick appearance in the urine, the evenness of blood pressure control with methyldopa in responsive patients is all the more striking. Obviously, the effect on blood pressure is not a function of blood level of the compound at a given moment. Thus, methyldopa itself may be looked upon as a ‘hit and run’ drug, the major question being which aspect of its action or metabolism accounts for a persistence of clinical effect, has to be researched upon [13].

Cortisone

Cortisone is a steroid hormone first produced in 1949 and found to act by modulating intracellular transcription processes which result in the activation or suppression of secondary mediators which affect many body functions. These actions prevail even after the elimination of the drug owing to the ‘hit and run’ effect [3].

Prostacyclin

Prostacyclin (PGI₂) is a member of the family of lipid molecules known as eicosanoids. The structure activity relationship studies have revealed that PGI₂ has ‘hit and run’ effects on some organs [27] mainly due to its action on cyclic nucleotides [14]. It has a strong effect on the cyclic nucleotide content of the rat gastric mucosa. One minute after an intragastric application of 100mcg/kg PGI₂ the cAMP content and in the 5th minute the cGMP-content showed a
highly significant decrease. It seems that the basic mechanism of action of PGI₂ is a typical ‘hit and run’ effect, acting on the intracellular second messenger system [14]. However, much has to be researched to identify the minute details of this action on the various organs and their messenger systems.

**Aminoglycosides**

These drugs also possess a unique pharmacokinetic profile, i.e. despite their short half life their antibacterial action lasts long. This is the “post antibiotic effect” attributed to the ‘hit and run’ effect of these drugs where the peak plasma concentration correlates with the bactericidal action but not the duration of action [16].

<table>
<thead>
<tr>
<th>Name of the Drug</th>
<th>Category</th>
<th>Mechanism of action</th>
<th>t½(hrs)</th>
<th>Duration of action</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reserpine</td>
<td>Adrenergic neuron blocking agent</td>
<td>Blocks the ability of aminergic transmitter vesicles to take up &amp; store biogenic amines.</td>
<td>24-28</td>
<td>386</td>
<td>Used as antihypertensive (rarely now), dyskinesia &amp; Huntington’s disease.</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Proton pump inhibitor</td>
<td>Block the final common pathway of acid secretion in parietal cells.</td>
<td>0.5–1.5</td>
<td>72</td>
<td>Used in peptic, gastric, duodenal ulcers and GERD.</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Centrally acting sympatholytic drug</td>
<td>Activates α₂ adrenoceptors.</td>
<td>2</td>
<td>24-26</td>
<td>Used to treat Hypertension</td>
</tr>
<tr>
<td>MAOIs</td>
<td>MAO-B inhibitor</td>
<td>Irreversible blockade of MAO-B.</td>
<td>1.5</td>
<td></td>
<td>Major depression unresponsive to other drugs.</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>Synthetic analog of vasopressin (DDVAP)</td>
<td>Antidiuretic action by activating G protein-coupled receptors vascular smooth muscles &amp; renal tubule cells.</td>
<td>1.5–2.5</td>
<td>6-20</td>
<td>Used to treat pituitary diabetes insipidus, coagulopathy in hemophilia A &amp; von Willebrand’s disease.</td>
</tr>
<tr>
<td>Cortisone</td>
<td>Glucocorticoid</td>
<td>Act on glucocorticoid receptors to regulate transcription of target genes.</td>
<td>8-12</td>
<td></td>
<td>Used to relive short term pain, reduce the the swelling from inflammation of joints, tendon and to treat sever sore throat.</td>
</tr>
<tr>
<td>Cocaine</td>
<td>CA reuptake Inhibitor</td>
<td>Inhibition of transmitter reuptake at noradrenergic synapse</td>
<td>1</td>
<td>2</td>
<td>Was used as local anaesthetic.</td>
</tr>
<tr>
<td>Aspirin</td>
<td>NSAIDS (non selective COX inhibitor)</td>
<td>Irreversibly inhibit platelet COX.</td>
<td>0.25</td>
<td>168</td>
<td>Used as analgesic &amp; antipyretic. Also in acute rheumatoid arthritis, post myocardial infarction, etc.</td>
</tr>
</tbody>
</table>

Table 1. The mechanism of action, t½ and uses of ‘hit and run’ drugs.
CONCLUSION

The pharmacokinetics and dynamics of ‘hit and run’ drugs outlines many clinical implications.

a. The duration of action of the drug may be longer than the actual stay of the drug in the body due to this ‘hit and run’ effect as in case of Reserpine and Omeprazole.

b. The pharmacodynamic actions of ‘hit and run’ drugs may be due to some irreversible or permanent changes in the enzymes or cellular functions as with aspirin, MAOIs and cortisone.

c. The ‘hit and run’ effect may be responsible for some ADR or may even be the reason for a lesser risk of a particular ADR. E.g. DDVAP and atypical antipsychotics.

d. The ‘hit and run’ effect may be seen with the parent compound but may not be seen with the metabolite e.g. selegiline.

e. ‘Hit and run’ effect of some drugs (cocaine) may cause euphorogenic effects.

f. The ‘hit and run’ effect may be responsible for the “post antibiotic effect” as with aminoglycosides.

However, a further research into the molecular aspects of many drugs with shorter stay but longer pharmacodynamic actions may throw light on various other aspects of ‘hit and run’ phenomenon.

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