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# To compare the simplicity and tolerability of two human models used for evaluation of anti-emetic drugs for severe vomiting

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## ABSTRACT

For evaluation of the antiemetic effects of the drugs animal models (Ferret,cat dog etc) are used. Although good guidelines may be established through the animal experiments, they may not give accurate indication of the antiemetic effect of the antiemetic drugs in patients due to species differences in pharmacokinetic and pharmacodynamic responses. Therefore, Ipecacuanha-induced emesis and flare models are used to predict more accurately the antiemetic effect of the antiemetic drugs. In ipecacuanha-induced emesis model in 10 healthy human volunteers slow intravenous injection of ondanserton -2 ml. (4 mg) was given over 5 minutes.Thirty minutes after inj. ondanserton, 30 ml. oral syrup of tincture ipecac was given with glassful of water. Then the parameters like time, number and duration of emesis were noted over 6 hour's period. In flare model in 6 healthy human volunteers Injection Serotonin 0.05 ml of 12.98 µM was given intradermally on the flexor aspect of forearm. Resulting flare response was measured over 5 minutes. At the end of half an hour, injection ondansetron and same dose of injection serotonin was given intradermally. Resulting flare response was measured in the similar way. Out of these two models, ipecac model is technically easy and clinically relevant but its tolerability is less. Flare model has excellent tolerability but it is technically not very easy. Thus one can choose the effective model accordingly.

**Key words:** Antiemetic, Ipecacuanha, Ondansetron, Serotonin

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## INTRODUCTION

Among the symptoms presented by the patients seen in the practice of gastroenterology, vomiting ranks second only to the pain in frequency of occurrence. It is an objective phenomenon and lends itself to the clinical study without great difficulty.[1] Emesis or vomiting is life saving as it quickly expels harmful materials from gastrointestinal tract.[2] Nausea is a psychic subjective experience with its somatic components often poses a greater clinical problem.[3]

Initial study of antiemetic agents is best performed in the presence of acute vomiting. It is limited to the short-term administration of drug alone, permitting identification of the dosage, toxicity and undesirable side effects, in addition to the preliminary observation of clinical effectiveness.[1,4]

For evaluation of the antiemetic effects of the drugs, animal models (ferret, cat, dog etc) are used. Although good guidelines may be established through the animal experiments, they may not give accurate indication of the antiemetic effect of the antiemetic drugs in patients due to species differences in pharmacokinetic and pharmacodynamic responses.

Therefore, Ipecacuanha-induced emesis model(antagonism of ipecacuanha induced emesis) and flare model(antagonism of the flare response to intradermal 5HT), these two models are used to predict more accurately the antiemetic effect of the antiemetic drugs.[5,6]

The ipecacuanha-induced emesis model has less tolerability. Tachyphlaxis to more doses of ipecac (in ferrets) and habituation to more than two doses of ipecacuanha may occur. Therefore many human volunteers are required for the study.[5,6] Validation of the ipecac-model and flare model is limited. No studies so far combined these two models together.[5] Therefore the present study is undertaken to study the relative ease of conduct and acceptable safety profile.

Selective 5-HT3 receptor antagonist Ondansetron is commonly used antiemetic drug in preventing nausea and vomiting associated with chemotherapy, radiotherapy and surgery. This drug is used in these two human models to compare the simplicity and tolerability between them.[3,5,7]

## MATERIALS AND METHODS

Approval was taken by (IEC) Institutional ethics committee, B. J. Medical college, Pune, Maharashtra, India.

**Ipecacuanha –Induced Emesis Model**

Study of this model was carried out in 10 healthy human volunteers. Routine health check up was done. Written informed consent and relevant history was taken. Subjects with history of

gastric problems were excluded from the study. Volunteers were kept nil by mouth since morning on the test day.

**Material**:

Following drugs were used in this test:

1. Injection Ondanserton (Hydrochloride dihydrate)
   (Emeset –Cipla) 4 mg - single dose)
2. Tincture ipecacuanha (General Pharmaceutical & Chemical Work)– 460 ml/bottle- 30 ml. single dose.

**Method:**

Slow intravenous injection of ondanserton -2 ml. (4 mg) was given over 5 minutes. 30 minutes after inj. ondanserton, 30 ml. oral syrup of tincture ipecac was given with glassful of water.

Parameters used were:

1. Time of onset of emesis (vomiting)
2. Number of episodes of vomiting
3. Duration of emesis
4. Adverse effects – if any
5. Severity of nausea assessed by using Visual analogue scale 0-100 mm) for rating of nausea.

These parameters were noted over 6 hour's period. All the volunteers were asked to mark the symptom-check list to assess the adverse effects, if any. The whole study was conducted in Ruby Hall Clinic, Pune. Results were tabulated and analyzed by Pie diagram.

**Flare Model**

This study was conducted in 6 healthy human volunteers. Written informed consent was taken prior to the test. Relevant history was taken regarding eczema, skin infection, etc.

**Material**:

Chemical used in this model was: Serotonin creatinine sulphate complex (Sigma)250 mg powder (molecular weight :387.4 gms),12.98 µM per 0.05 ml was prepared in sterile water for injection. Drug used was – Injection ondanserton hysrochloride dihydrate (2 mg/ml Emset-Cipla)

**Method:**

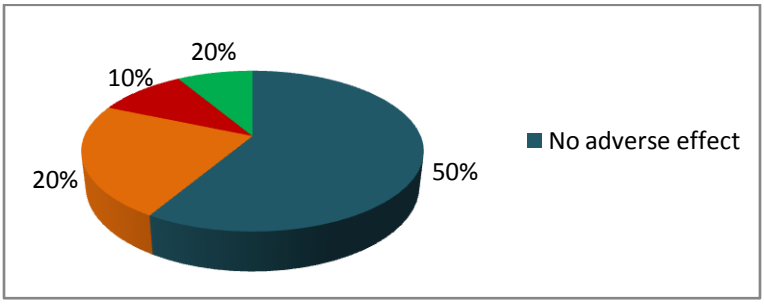
Injection Serotonin 0.05 ml of 12.98 µM was given intradermally on the flexor aspect of forearm with conventional insulin syringe (28 G) using full aseptic precautions. Resulting flare response was measured over 5 minutes over 5 minutes upto 30 minutes with measuring scale in millimeters. At the end of half an hour, injection ondanserton, same dose of injection serotonin

was given intradermally.Resulting flare response was measured in the similar way. Results were tabulated and analyzed by paired 't' test.

## RESULTS AND DISCUSSION

### Ipecacuanha –Induced Emesis Model

All the volunteers were observed for 6 hour period for the emetic response and adverse events, if any, There were no emetic episodes (Table-I) when tincture ipecac was given after ondanserton 4 mg. Only 20% subjects suffered from abdominal discomfort (Graph – I).




=Nausea, abdominal discomfort = Sedation = Headache

**Graph I:Ipecacuanha-induced emesis model**

**Table I :Ipecacuanha-Induced Emesis Model**

| No. | Time of onset of emesis | Duration of emesis | No. of emetic episodes | Rating of nausea VAS 0-100 mm | Adverse effects over 6 hours period |
|---|---|---|---|---|---|
| 1 | - | - | 0 | 36 mm | Abdominal discomfort & nausea |
| 2 | - | - | 0 | 0 mm | - |
| 3 | - | - | 0 | 0 mm | Headache |
| 4 | - | - | 0 | 0 mm | - |
| 5 | - | - | 0 | 10 mm | Abdominal discomfort & nausea |
| 6 | - | - | 0 | 0 mm | - |
| 7 | - | - | 0 | 0 mm | Headache |
| 8 | - | - | 0 | 0 mm | |
| 9 | - | - | 0 | 0 mm | |
| 10 | - | - | 0 | 0 mm | Sedation |

- = Absent/ No emesis

0 = No any episode of vomiting

VAS - Visual Analogue Scale

Nausea was noted using visual analogue scale (0-100 mm). Median peak nausea scores were 0 mm in 80% subjects, 10 mm in 10% subjects and 36 mm in 10% subjects. Nausea occurred principally in those subjects, suffering from abdominal discomfort and only 1 subject required rescue medication (i.e. Tab. metoclopramide 10 mg – in the evening – due to nausea .Only 20%

subjects suffered from headache. Sedation occurred only in 10% volunteers.

From the observations above of ipecacuanha-induced emesis model it appeared that there are no episodes of vomiting after ondanserton within an observation period of 6 hrs. Mild nausea with abdominal discomfort, headache and sedation was noted in few subjects.

From the study of this model, it can be said that antagonism of the emetic response by 5-$HT_3$ receptor antagonist ondanserton may be due to its peripheral action at abdominal visceral afferent neurons or central action within the area postrema and tractus solitarious or combination of these.[8] Ipecacuanha is a potent emetic containing the principal active ingredients, emetine and cephaeline. It can produce vomiting within 15-30 mins , because of its local irritant action on enteric tract and on chemoreceptor trigger zone (CTZ) in area postrema of the medulla.[9] This model has the advantage of being more conceptually relevant than the flare model. Technically this model is simple and cheap. It can be used to predict more accurately clinically effective antiemetic doses of 5-$HT_3$ receptor antagonists.[10]

The main disadvantage of this model was that ipecac can be administrated to each volunteer only once, as it was known to produce anticipatory vomiting, habituation and tachyphylaxis when administrated in more than two occasions. Validation of this model is limited.[8] Mild adverse events like abdominal discomfort with nausea in 20% subjects, headache in 20% subjects and sedation in 10% subjects were observed in our study. Only one subject required rescue medication, i.e. Tab. metoclopramide 10 mg orally only once. This model has less tolerability.Thus, it can be said that for studying the antiemetic effect of the anti-emetic drugs, this model is very useful even though it has less tolerability.

**Flare Model**

Ondensation 4 mg reduced the size of the flare. There was diminishing effect on the flare response over the 5, 10, 15, 20, 25 & 30 mins. following post-dose 5-HT (serotonin) injections. All the subjects experienced transient local tingling, stinging sensation and mild pain which were diminished within few seconds. Mean flare size before and after ondanserton is shown in (Table – II & Graph-II).It indicates that there is statistically significant reduction in flare size ($P<0.001$) after administration of ondanserton.

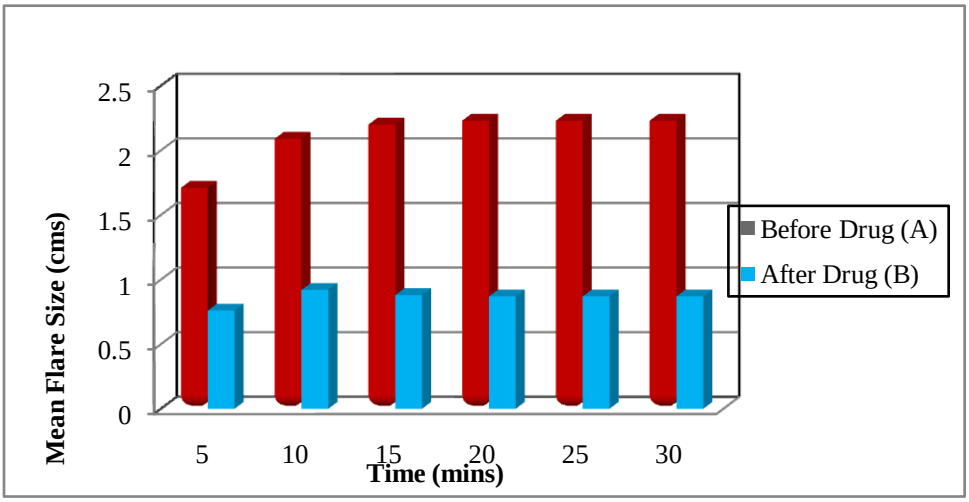
In the study of flare model, it was observed that there is considerable reduction in the flare response to intra-dermal serotonin after giving ondansetron. From the study of this model it can be said that intra-dermal injection of 5-HT produces a flare response which is thought to be mediated by excitation of 5-$HT_3$ receptors on cutaneous afferent neurons. Stimulation of these

receptors causes the release of substance P, via an axon reflex, resulting in vasodilatation with subsequent erythema or flare which was reduced ondansetron[8]

**Table II: Flare Model**

| No. | Time (mins.) | Mean Flare Size (cms) | |
|---|---|---|---|
| | | Before Drug (A) | After Drug (B) |
| 1 | 5 mins. | 1.71±0.21 | 0.76**±0.21 |
| 2 | 10 mins. | 2.09±0.10 | 0.92**±0.77 |
| 3 | 15 mins. | 2.20±0.13 | 0.88**±0.13 |
| 4 | 20 mins. | 2.23±0.10 | 0.87**±0.07 |
| 5 | 25 mins. | 2.23±0.10 | 0.87**±0.07 |
| 6 | 30 mins. | 2.24±0.10 | 0.87**±0.07 |

Results are expressed as Mean ± s.d. ** - P < 0.001




**Graph II: Flare model**

The flare model have the advantage of simplicity and excellent tolerability. However, this model is technically not very easy as it is difficult to standardize the angle, depth and rate of intra-dermal injection with the conventional insulin syringe. Hence, can produce variable results.[6,8]

Special device, i.e. auto-injector is required which is specially designed to deliver the drug at a constant rate and to a predetermined depth. Depth of needle can be preset using a flange according to the thickness of epidermis (0.06-0.1 mm on most of the body and 4 mm on back). This device can give repeatable, acceptable, convenient, less painful and smaller response than the insulin syringe. But this method is costly as an auto-injector device and serotinine creatinine sulphate powder, both are costly.[6]

Mild adverse events such as transient local tingling or stinging sensation was experienced by the subjects which lasts only for few seconds.[8]

However, the relevance of inhibition of the flare response as a predictive model of antiemetic activity is questionable in view of its apparent discrepancy in duration of pharmacological

activity.[11,12] So, it can be said that for studying the antiemetic drugs, this model is useful as it has excellent tolerability.

## CONCLUSION

In ipecacuanha-induced emesis model, ondansetron antagonizes the emetic action of ipecac. Even if this model is technically easy and clinically relevant, the tolerability of the ipecacuanha – induced emesis model is less as compared to flare model due to its adverse events like abdominal discomfort, sedation and nausea and headache ,etc. In flare model ondansetron antagonizes the flare response induced by serotonin. This model has excellent tolerability than ipecacuanha-induced emesis model because of its negligible adverse effects such as local stinging or tingling sensation and mild pain of short duration, i.e. only for few seconds. But this model is technically difficult as accidental subcutaneous penetration may occur while giving intra-dermal injection of serotonin which can produce severe adverse effects like hypotension, bradycardia, etc. Thus , our study suggests that, even though ipecacuanha-induced emesis model is technically easy and clinically relevant, its tolerability is less as compared to flare model because of the adverse effects. Flare model has excellent tolerability but it is technically not very easy.

For the evaluation of the antiemetic drugs for severe vomiting, e.g. $5HT_3$ receptor antagonists, Dopamine receptor antagonists etc., ipecacuanha-induced emesis model is clinically more relevant than the flare model even though it has less tolerability. Thus, one can choose the effective model accordingly.

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