Facts on

Novalgin®

Active ingredient: Analgin

Baralgan®

Active ingredient:
Analgin
Fenpiverinium Bromide
Pitofenone Hydrochloride

Hoechst

19/6/1989

CONTENTS

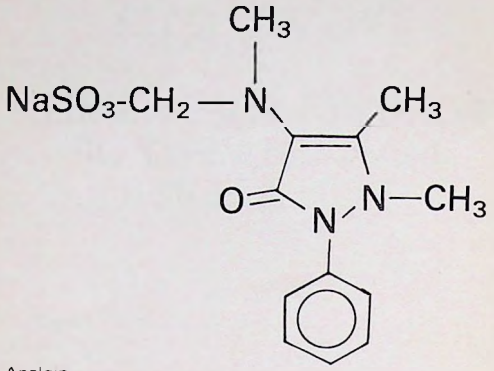
Novalgin®

Active ingredient: Analgin

FOR THE RESPONSIBLE MANAGEMENT OF PAIN & FEVER

PAIN

FEVER

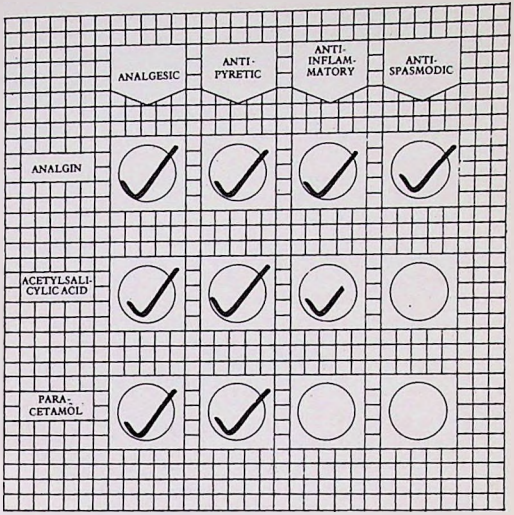


Analgin
Noraminopyrine methane sulphonate
Metamizol sodium

Novalgin (analgin) is a non-narcotic analgesic, which was first introduced to medicine in 1922. It was developed as an improved derivative of pyramidon (aminopyrine, aminophenazone) and differs from the parent substance both in terms of toxicity and in terms of its medicinal potential.

Novalgin has several distinguishing characteristics.

- It has strong analgesic and antipyretic effects as well as anti-inflammatory and antispasmodic properties. This latter effect distinguishes Novalgin from all other non-narcotic analgesics.



Novalgin is an outstanding analgesic and antipyretic. In addition to its anti-inflammatory effects Novalgin is the only substance with antispasmodic effects (30).

- Novalgin's high water solubility has led to a wide variety of administration forms, including the rapidly acting injectable formulations. The injection has rapid and potent analgesic and antipyretic effects. In indications such as post-operative pain or carcinoma pain, Novalgin is a suitable alternative to administration of opiates.

- Novalgin has the lowest toxic potential of all non-narcotic analgesics. It is also less likely to adversely affect the liver, kidneys or gastro-intestinal mucosa.

Possibly owing to its general lack of toxic effects, Novalgin has been closely scrutinized with regard to hypersensitivity reactions. Its structural relationship to aminopyrine, which was considered to give rise to a high incidence of agranulocytosis, has led to the assumption that analgin shared this characteristic. Newer, more reliable data shows that whereas analgin is one of the over 100 drugs which can give rise to agranulocytosis, the likelihood is considerably lower than formerly postulated, and is no greater than equivalent risks associated with the use of other non-narcotic analgesics.

Each of the currently available non-narcotic analgesics has specific properties which render it hazardous in some patients while at the same time being irreplaceable in others.

Historical note

The currently available non-narcotic analgesics were all developed as synthetic alternatives to quinine, which was the natural antipyretic most commonly used in the nineteenth century.

The first non-narcotic analgesic to find widespread acceptance was Antipyrine (phenazone), a pyrazolone derivative, which was developed by Hoechst in 1884. Further work on this class of compounds led to Pyramidon (aminopyrine, aminophenazone) in 1897. More than three decades of research were required at Hoechst for the subsequent development of Novalgin (analgin), which was introduced in Germany in 1922.

Despite its close chemical relationship to its precursor Pyramidon, Novalgin differs in terms of its physical properties, pharmacological effects and toxicology. Novalgin is, for example, considerably less toxic and cannot give rise to dimethyl nitrosamine (the reason for Pyramidon's disappearance from modern medicine) (1). Novalgin is also characterized by greater therapeutic versatility than its precursor, and all other non-narcotic analgesics.

Novalgin is highly water-soluble. It also has the widest safety margin of all non-narcotic analgesics. These qualities permit use of a 50% solution of analgin for intramuscular or intravenous injection. In this form Novalgin transcends the ceiling effects of non-narcotic analgesics and, for many indications, becomes an alternative to opiates.

Pharmacological properties

Novalgin has analgesic, antipyretic and anti-inflammatory effects. Unlike other non-narcotic analgesics, it also has antispasmodic properties.

Like other non-narcotic analgesics, Novalgin's analgesic, antipyretic and anti-inflammatory effects result from inhibition of prostaglandin biosynthesis. Novalgin's antispasmodic property derives from a direct relaxant effect on visceral smooth muscle. Unlike acetylsalicylic acid, Novalgin does not bind cyclo-oxygenase (prostaglandin synthetase) irreversibly.

Pharmacological studies have shown that Novalgin inhibits prostaglandin synthesis most markedly in brain tissues. This may explain its potent analgesic and antipyretic effects (2).

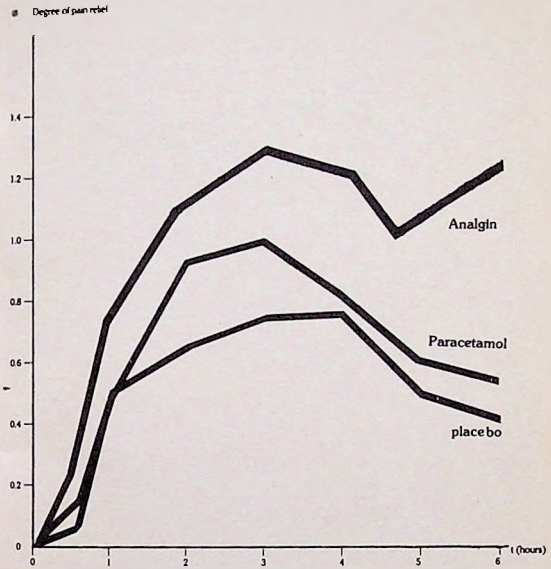
The effects of the non-narcotic analgesics differ from substance to substance. This may be partly explained by their differing concentrations in various tissues (2).

As opposed to acidic analgesics, non-acidic analgesics, such as analgin metabolites, do not accumulate in the gastric mucosa or in the renal cortex (2).

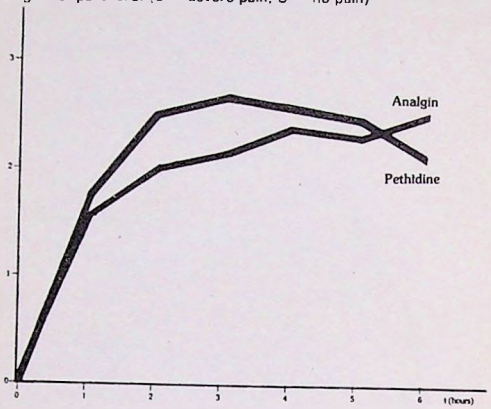
In addition, unlike acetylsalicylic acid, Novalgin does not depress prostacyclin synthesis in the gastric mucosa. Novalgin has only a weak inhibitory effect on renal cyclo-oxygenase (3).

The above findings explain how Novalgin is so well tolerated by the gastro-intestinal mucosa and the kidneys. Toxicological testing has also confirmed that Novalgin is extremely well tolerated by the liver (4).

Neither analgin nor its metabolites affect the lipoxygenase pathway. Thus there is no production of leukotrienes (5).



In a placebo-controlled double-blind study on 299 patients with initial severe pain after episiotomy, analgin provided stronger analgesia than the same dosage of paracetamol (1 x 500 mg p.o.) Analgin achieved statistically significant superiority over placebo within half an hour (6).



In a double-blind comparative study, 51 patients received 2.5 g analgin i.m. (corresponding to 1 ampoule Novalgin 5 ml) and 49 patients received 100 mg pethidine i.m. They were suffering from pain of moderate to severe intensity after exploratory laparotomy. Both groups were comparable in terms of the onset, intensity and duration of pain relief (11)

Clinical results

Novalgin is effective in a wide range of pain conditions, e.g., from headache to post-operative pain, as confirmed repeatedly during the six decades since its introduction to medicine (6, 7, 8, 9, 10, 11).

When injected, its potency is comparable to pethidine (11, 12) or dextropropoxyphene (13).

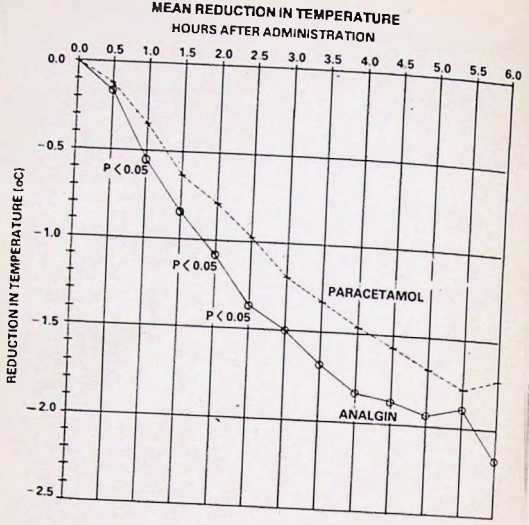
In pain due to malignant diseases, Novalgin may be used to delay the administration of opiates or to reduce the dosage of opiate required (14).

Analgin has undisputed advantages in the treatment of smooth muscle spasm (7) and potentiates the therapeutic effects of pure antispasmodic substances. Alone or in combination it is more suited to the treatment of renal or biliary colic than opiates, which have spasmogenic effects. Analgin also lacks the tendency of opiates to induce respiratory depression or constipation. Analgin has no euphoric potential and does not lead to habituation.

Novalgin's antipyretic effects are potent, and Novalgin is effective even in cases where other measures have failed (14). Novalgin has been shown to be a more effective antipyretic than other non-narcotic analgesics (15, 31).

Novalgin's low toxic potential and high efficacy recommend it to paediatric use. Clinical trials in children (32) have shown that there is no effect on normal body temperature.

Novalgin also has a long duration of action (up to 6-8 hours). This avoids fever spikes during the night and therefore, allows sick children to enjoy a full night's rest



In a double-blind study comparing 500 mg of analgin with 500 mg of paracetamol in 53 patients suffering from typhoid fever, it was seen that

1. Analgin causes significantly higher reduction in temperature
2. The onset of action is significantly faster with analgin
3. The total antipyretic effect is significantly higher compared to paracetamol (16)

Safety data

Analgin has been in use since 1922 and is currently being used in over 100 countries. Based on the WHO Daily defined dose (1.5 g per patient per day) almost 20 million patients are treated with analgin every day. A vast amount of experience has, therefore, been accumulated.

Analgin's wide safety margin is undisputed and is unequalled by other non-narcotic analgesics. Few cases of toxicity due to accidental or deliberate overdosage have ever been seen. A published case report describes an 18 year old girl who took 98 tablets of Novalgin (equivalent to 49 g or more than 10 times the recommended daily dose). Apart from transient nausea and vomiting there were no toxic symptoms whatsoever. Nor were there any after effects on circulation, central nervous system, liver, kidneys or any other organs (18).

The data available also demonstrates that no relevant renal (19) or hepatic adverse effects have been seen. This evidence is also supported by toxicological data.

Hypersensitivity reactions

In spite of the vast amount of evidence demonstrating Novalgin's excellent tolerability it has been subject to (often very vague) discussion concerning two groups of hypersensitivity reactions.

One of these reaction types are the anaphylactoid reactions (analgesic asthma/analgesic intolerance). As with other prostaglandin synthetase inhibitors, analgin can give rise to anaphylactoid reactions characterzied by rhinitis, conjunctivitis, urticaria, angio-oedema, bronchial asthma and possibly shock.

As would be expected, shock is the most alarming of the anaphylactoid reactions. It is very rare and is generally associated with too rapid injection, though some cases probably represent genuine anaphylaxis.

As Novalgin injection contains a 50% solution of analgin, it is necessary that the injection be given very slowly (1 ml per minute). The advantages which the injection formulation offers (rapid action and high potency) are in no way dissipated by the need for slow injection.

The other hypersensitivity reaction discussed with regard to Novalgin is agranulocytosis (20). Here it must be remembered that Novalgin is chemically related to aminopyrine, which was one of the first drugs to be associated with agranulocytosis (21). However, even for aminopyrine, the postulated incidence of this reaction was always subject to speculation, and was not based on acceptable scientific data (by modern standards). Patients who developed agranulocytosis had invariably taken several drugs (this also holds true today), and attribution of blame was usually an act of faith. For analgin itself there was an almost complete lack of relevant data.

It was for clarification of this issue that Hoechst agreed to co-finance an international study on the incidence of blood dyscrasias called the International Agranulocytosis and Aplastic Anaemia Study.

The International Agranulocytosis and Aplastic Anaemia Study (22)

This study was carried out in 7 countries and monitored some 22 million people for a 5-year period. The design of the study (case-control method) provided for a control group and allowed for mathematical calculation of the likelihood of causality. As such, this study (which was run by the Drug Epidemiology Unit of Boston Medical School) broke new ground in the study of blood dyscrasias.

Among the findings are the fact that (23):
Agranulocytosis is a rare event. On average only six cases occur per million persons per year.
Agranulocytosis has a survival rate of over 90%.

The primary risk group are persons over 60 years of age with multiple drug use, particularly if they are female (twice as frequently as males). The risk decreases exponentially towards younger age groups, so that children are hardly at risk.

Of the more than 100 drugs potentially associated with agranulocytosis, treatment with analgin was found to involve an excess risk, if any, of at most 1 in a million (24) users/week/year, which gives an incidence rate as low as 0.0001%!

Other recent safety data

Novalgin is very unlikely to give rise to interactions due to its low plasma protein binding (60%) (25). There is no interaction with anticoagulants (26), with alcohol (27) or with antidiabetic drugs (28).

It has also been estalished that Novalgin s metabolites only pass in very small quantities into human breast milk (29) and are no longer detectable 48 hours after drug administration.

PRESCRIBING INFORMATION

Novalgin®

COMPOSITION

Tablets

Each tablet contains:
Analgin I.P. ..... 0.5 g.

Injection

Each ml contains:
Analgin I.P. ..... 0.5 g.

PROPERTIES

Novalgin is a non-narcotic analgesic, antipyretic, anti-inflammatory and antispasmodic agent.

As Novalgin can be injected intravenously, it is possible to obtain extremely potent analgesia in a variety of conditions and thus to control pain which would otherwise respond only to opiates.

Even in high doses, Novalgin, unlike opiates, does not cause either addiction or respiratory depression. It does not impair peristalsis of the intestine, labour contractions or renal and biliary stone elimination.

INDICATIONS

For the Relief of Pain

Novlgin is indicated for all types of pain like headaches, neuralgia, muscle pain, arthralgia, post-operative pain, traumatic pain associated with burns, injuries, fractures, dental procedures, etc.

For the Relief of Fever

For lowering raised temperature in febrile diseases as well as in cases of high fever which do not respond to other measures.

ADMINISTRATION AND DOSAGE

In mild and moderate pain, the oral route is generally adequate. In acute painful conditions requiring rapid relief, the parenteral (i.m. or i.v.) route should be preferred.

Generally, the following dosage is recommended

Tablets

Adults and adolescents over 15 years

An initial dose of 1-2 tablets followed by 1 tablet 3-4 times daily is recommended

Children

In the age group between 5-14 years the dose is calculated on the basis of approximately 30-60 mg/kg body weight per day in divided doses.

5 — 7 years	½ — 1 tablet	up to a total of 2 tablets/day
8 — 11 years	½ — 1 tablet	up to a total of 3 tablets/day
12 — 14 years	1 to 1½ tablet	up to a total of 4 tablets/day

Injections:

Intravenous injections must be administered slowly (not more than 1 ml per minute) with the patient lying down; attention must be given to cardiovascular functions. In patients with hypersensitivity reactions of any type, also to substances other than drugs, it is recommended to stop the injection after 0.1-0.2 ml and to observe the reaction of the patient for 1 to 2 minutes.

The injection should be administered with the solution warmed to body temperature

In adults, an initial **intravenous** dose of 1-2 ml. is recommended. The daily dose may, if necessary, be increased to 5 ml. in divided doses.

The average adult **intramuscular** daily dose is 2 ml. 2-3 times daily. The solution should be brought to body temperature and should be slowly injected into the gluteal muscle.

Age of patient	Smallest single dose i.m./i.v.	Maximum daily dose i.m./i.v.
Adults and adolescents aged 15 years or over	2 ml.	5 ml.
Children (1-14 years)		
1-2 years	0.2 ml.	4 x 0.4 ml.
3-4 years	0.2 ml.	4 x 0.6 ml.
5-7 years	0.4 ml.	4 x 0.8 ml.
8-11 years	0.5 ml.	4 x 1.0 ml.
12-14 years	0.8 ml.	4 x 1.2 ml.

Intramuscular injection only

Infants	Smallest Single dose	Maximum daily dose
3-5 months	0.1 ml.	4 x 0.2 ml.
6-11 months	0.1 ml.	4 x 0.3 ml.

CONTRAINDICATIONS

Novalgin must not be used in patients with pyrazolone allergy, collapse states, hepatic porphyria or congenital glucose-6 phosphate dehydrogenase deficiency.

PRECAUTIONS

During pregnancy, particularly the first three months and the last six weeks, in infants less than three months old or weighing less than 5 kg, and in patients with disorders of haematopoiesis. Novalgin should only be employed, if strictly indicated or prescribed by a doctor.

SIDE EFFECTS

The more important but rare side effects of pyrazolone preparations, such as Novalgin, arise from hypersensitivity reactions. The most serious reaction is a reduction in the number of white blood cells (granulocytopenia) or their complete disappearance (agranulocytosis). Therefore, if there is an unexpected deterioration in the patient's general condition, if the fever fails to subside or recurs, if painful mucous membrane changes occur, especially in the mouth and throat, it is essential to discontinue Novalgin immediately and consult a doctor. Symptoms are febrile infections with predominant localisation in the skin-mucous membrane boderline regions. If agranulocytosis is suspected, blood counts must be performed. After immediate discontinuation of Novalgin and under protective treatment (mainly with antibiotics) regeneration of the leucocytes is to be expected.

Occasionally, hypersensitivity reactions manifesting in the skin and the mucous membranes of the eyes and the nose throat region may occur.

Shock is the other serious but rare hypersensitivity reaction mainly after parenteral administration. Its first signs are pruritus, cold sweat, dizziness, stupor, nausea, flushing or pallor of the skin, dyspnoea. If they occur, medical help must be called in without delay. Until the doctor arrives, ensure that the patient is kept flat with legs raised and airways patent.

The signs of imminent shock may appear already during the injection. In this case, interrupt the injection immediately, leave the venous cannula in place or perform venous cannulation, ensure that the patient is kept flat with the legs raised and airways patent and immediately adopt standard emergency procedures for shock treatment.

SPECIAL NOTES

Patients who suffer from bronchial asthma or chronic respiratory infections and patients with hypersensitivity reactions also to substances other than drugs belong to a risk group which, on using analgesic or antirheumatic agents of all kinds, may develope shock (analgesic intolerance). They should consult the doctor before taking such drugs.

A red coloration of the urine may be seen. It is due to excretion of a harmless metabolite of Novalgin and disappears after the end of the treatment.

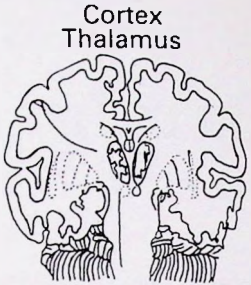
Analgesics must not be used in high doses or over prolonged periods of time without the doctor's advice

Novalgin must not be mixed with other drugs in the syringe

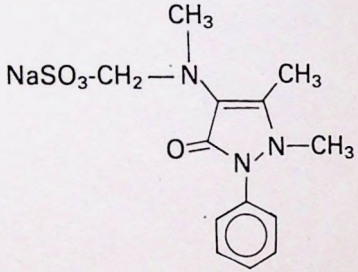
Baralgan®

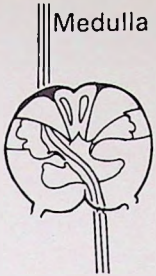
Active ingredients Analgin
Fenpivernium Bromide
Pitofenone Hydrochloride

Your sure answer to spasmodic pain

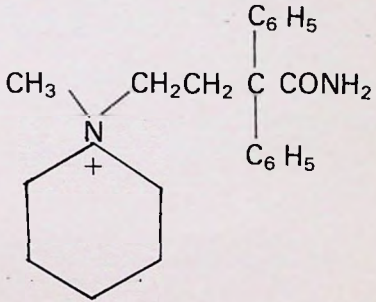


At the level of pain integration by the constituent analgin

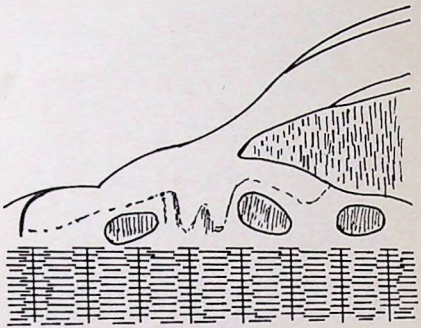




At the level of the pyramidal decussation (cholinergic fibres) by the constituent fenpiverinium bromide

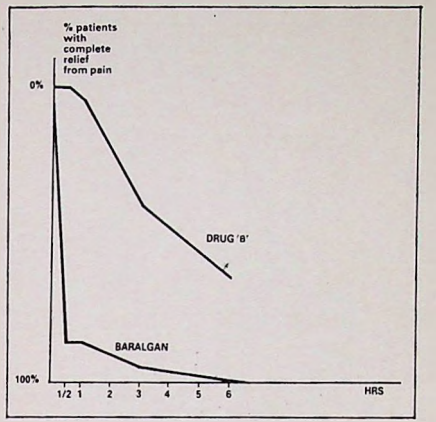


Viscera



At the level of the end plate of cholinergic nerve fibres by the constituent pitofenone hydrochloride

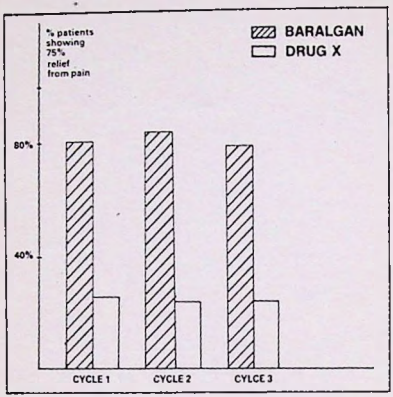
CLINICAL RESULTS



Baralgan provides rapid relief in colicky pain

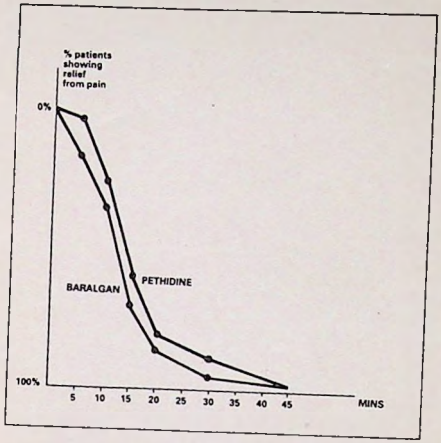
In a trial of patients with intestinal or renal colic, 40 patients were given Baralgan 5 ml. (corresponding to analgin 2.5 g., fenpiverinium bromide 0.1 mg. pitofenone hydrochloride 10 mg.)

While 28 patients were given Drug 'B' 3 ml (corresponding to 72 mg. of avapyrazone and 720 mg of analgin), within 30 minutes, 85% of patients with intestinal colic were relieved after Baralgan, as against none with Drug 'B' (33).



Baralgan provides long-lasting relief, cycle after cycle, in spasmodic dysmenorrhoea

In primary dysmenorrhoea Baralgan (1 tablet = analgin 0.5 gm., fenpiverinium bromide 0.1 mg., pitofenone hydrochloride 5 mg.) was found to be significantly superior to Drug 'X' (1 cap = dicyclomine hydrochloride 10 mg. dextropropoxyphene hydrochloride 65 mg., acetaminophen 400 mg., chlordiazepoxide 5 mg.). In the cross-over phase of the study, 84% of patients on Drug 'X' were further relieved by Baralgan. However, when patients were switched from Baralgan to Drug 'X', no significant improvement occurred (34).



Baralgan provides rapid action in renal colic comparabale with that of opiates.

In a comparative trial of Baralgan (3 ml. i.v. along with 2 ml. i.m.) and pethidine (50-100 mg.) in renal colic, 95% of patients were relieved within 30 minutes after Baralgan, as compared to 87% patients who were relieved with pethidine.

Baralgan does not only combat pain effectively at the site of pain perception: but also acts on the cholinergic nerve fibres which are responsible for painful spasm.

Range of indications

Gastric colic
Intestinal colic
Biliary colic
Renal colic
Ureteric colic
Dysmenorrhoea
Pain associted with pancreatitis
Pain associated with neoplasms
Vasomotor headache
Post-operative pain & spasm
Preparation for surgery

PRESCRIBING INFORMATION

Baralgan®

COMPOSITION

	TABLETS Each Tab.	DROPS Each ml. (=30 drops)	INJECTIONS Each ml.
Analgin I.P.	0.5 g.	0.5 g.	0.5 g.
Pitofenone Hydrochloride	5.0 mg.	5.0 mg.	2.0 mg.
Fenpiverinium Bromide	0.1 mg.	0.1 mg.	0.02 mg.

PROPERTIES

Baralgan is ideally suited for the treatment of spasmodic pain because of its rapid and sustained antispasmodic effect on the smooth muscles. Even in very severe forms of spasmodic pain, Baralgan almost invariably renders the administration of opium alkaloids unnecessary.

Together with the analgesic and antispasmodic properties of analgin, Baralgan contains Pitofenone Hydrochloride, a papaverine-like compound as well as Fenpiverinium Bromide, a substance with parasympatholytic action which reinforces the spasmolytic effect.

INDICATIONS

Renal colic
Biliary colic
Painful spasmodic conditions of the gastrointestinal tract
Spasmodic dysmenorrhoea, and
Other painful conditions due to spasm of smooth musculature

ADMINISTRATION AND DOSAGE

Unless otherwise prescribed, the following doses are recommended

Tablets and drops

	Smallest single dose		Maximum daily dose	
	Tablets	Drops	Tablets	Drops
Adults and adolescents of 15 years or over	1	—	4 x 2	—
Infants and children				
3-5 months	—	3-6	—	4 x 6
6-11 months	—	4-9	—	4 x 9
1 year	—	5-11	—	4 x 11
2 years	—	6-12	—	4 x 12
3-4 years	—	8-18	—	4 x 18
5-7 years	½	—	4 x ½	—
8-11 years	½ tablet	—	4 x 1	—
12-14 years	1 tablet	—	4 x 1½	—

Injections

Baralgan injection must not be mixed with other drugs in the same syringe.

During intravenous injection which should be administered slowly (at a rate not exceeding 1 ml. per minute), with the patient lying down, attention must be given to cardiovascular functions. In patients with hypersensitivity reactions of any type, also to substances other than drugs, it is recommended to stop the injection after 0.1-0.2 ml. and to observe the reaction of the patient for 1 to 2 minutes.

The solution should be warmed to body temperature prior to injection.

Generally, the following dosage is recommended.

Adults

In case of spasmodic pain, slow intravenous injection of 2 ml. may suffice.

In acute severe colic, 5 ml. Baralgan should be administered by slow intravenous injection. This may be repeated twice daily if required.

In less severe cases Baralgan injection may be given intramuscularly (2-5 ml., 2-3 times a day). However, the total daily dose should not exceed 10 ml.

Children aged 1-14 years

	Smallest single dose i.m. or i.v.	Maximum daily dose i.m. or i.v.
1-2 years	0.2 ml.	4 x 0.4 ml.
3-4 years	0.2 ml.	4 x 0.6 ml.
5-7 years	0.4 ml.	4 x 0.8 ml.
8-11 years	0.5 ml.	4 x 1.0 ml.
12-14 years	0.8 ml.	4 x 1.2 ml.

Infants	Intramuscular injection only	
	Smallest single dose	Maximum daily dose
3-5 months	0.1 ml.	4 x 0.2 ml.
6-11 months	0.1 ml.	4 x 0.3 ml.

CONTRAINDICATIONS

Pyrazolone allergy, collapse states, hepatic porphyria, congenital glucose-6-phosphate dehydrogenase deficiency, tachyarrhythmia, narrow-angle glaucoma, prostatic hypertrophy with a tendency to urinary retention, gastrointestinal obstruction, megacolon.

PRECAUTIONS

Patients who suffer from bronchial asthma or chronic respiratory infections and patients with hypersensitivity reactions also to substances other than drugs belong to a risk group which, on using analgesics or antirheumatic agents of all kinds, may develop shock (analgesic intolerance). They should consult the doctor before taking such drugs. The same applies to patients who react to alcohol, even to small amounts with sneezing, running eyes and severe facial reddening.

During pregnancy, particularly the first three months and the last six weeks, as well as in infants less than three months old or weighing less than 5 kg, and in patients with disorders of haematopoiesis, Baralgan should only be administered if strictly indicated.

SIDE EFFECTS

On rare occasions hypersensitivity reactions may occur as for any pyrazolone derivative. Isolated instances of granulocytopenia or agranulocytosis have been reported. Hence, if there is an unexpected deterioration in the patient's general condition, if there is fever or if painful mucous membrane changes occur especially in the mouth and throat, it is essential to discontinue Baralgan immediately and consult the doctor. Symptoms are febrile infections with predominant localization in the skin-mucous membrane borderline regions. If agranulocytosis is suspected, blood counts must be performed. After immediate discontinuation of Baralgan and under protective treatment (mainly with antibiotics) regeneration of the leucocytes is to be expected.

Clinical features of shock may on rare occasions be observed following parenteral administration. The signs of imminent shock may appear already during the injection. In this case, interrupt the injection immediately, leave the venous cannula in place or perform venous cannulation, ensure that the patient is kept flat, the legs raised and airways patent and immediately adopt standard emergency procedures for shock treatment.

Occasionally, cutaneous or mucocutaneous hypersensitivity reactions of the eyes, nose and throat may occur.

Anticholinergic side effects such as dryness of the mouth, a decrease in perspiration, disorders of accommodation, accelerated heart rate and micturition difficulties are practically never seen, provided Baralgan is administered in recommended doses.

SPECIAL NOTES

Analgesics must not be used in high doses over prolonged periods of time without the doctor's advice.

Patients in whom Baralgan has caused a HYPERSENSITIVITY reaction of any type should avoid future use of all pyrazolone-containing preparations.

Red coloration of the urine may occasionally be seen. This is due to the excretion of rubazonic acid, a harmless metabolite of Baralgan.

The contents of the R.C. Vial are not recommended for intravenous administration.

INTERACTIONS

If quinidine is administered at the same time as Baralgan, a potentiation of the anticholinergic effect is possible. The patient must be warned that the effect is possible.

The patient must be warned that the effect of alcoholic beverages may be enhanced by Baralgan medication.

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