

Metamizol (Novalgin[®]) zur postoperativen Schmerztherapie: Bleibt alles beim Alten?

Update 2005

Prof. Klaus A. Lehmann
Klinik für Anesthesiologie und Operative Intensivmedizin
Universität zu Köln

Metamizol, Dipyrone (Novalgin[®])



Weltweite Verbreitung



Markteinführung 1922

nie zugelassen:
UK

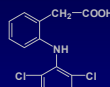
zurückgezogen:
USA 1977,
Schweden 1999

Verschreibungspflicht
in Deutschland
seit 1986, Verbot von
Kombinationspräparaten

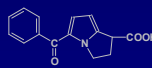
Injizierbare Nichtopioid-Analgetika (1)



Acetylsalicylsäure



Diclofenac



Ketorolac

Säuren (NSAIDs, NSAR)

- analgetisch
- antipyretisch
- antiphlogistisch

Hemmung der
Prostaglandinsynthese:
Gerinnung, Magen, Niere

Injizierbare Nichtopioid-Analgetika (2)



Paracetamol

Coxibe (spez. COX₂-Hemmer)

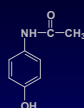
- analgetisch
- antipyretisch
- antiphlogistisch ?

analgetische Potenz,
Niere, Herz-Kreislauf ?



Valdecoxib

Injizierbare Nichtopioid-Analgetika (3)

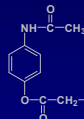


Paracetamol

Aniline

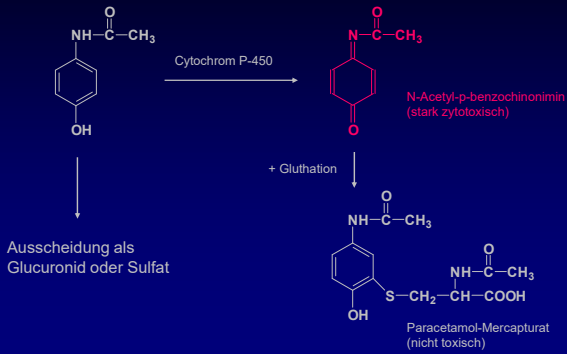
- analgetisch
- antipyretisch
- antiphlogistisch ?

analgetische Potenz,
Leber (bei > 4 g/d)



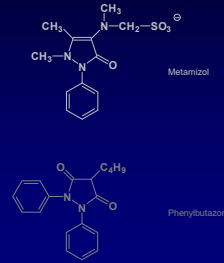
Propacetamol

Paracetamol-Metabolismus



Injizierbare Nichtopioid-Analgetika (4)

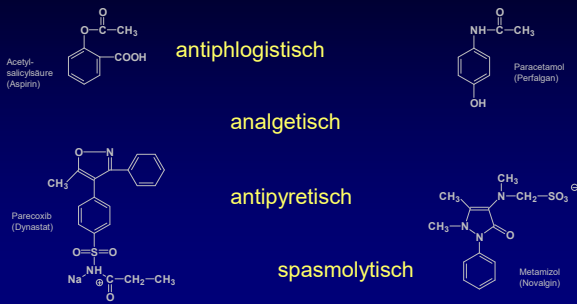
Pyrazolone



- analgetisch
- antipyretisch
- *spasmolytisch*

allergische Reaktionen,
Schock bei i.v.-Injektion,
Agranulozytose

Qual der Wahl

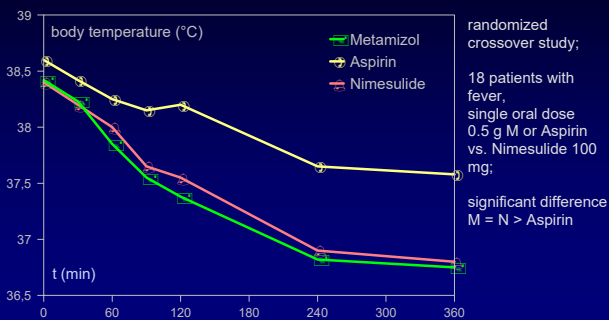


Qual der Wahl



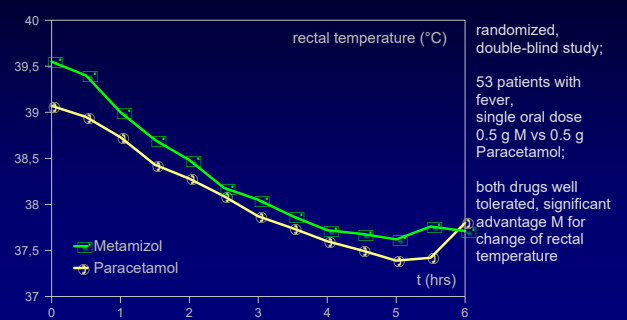
Nimesulide in the treatment of fever: a double-blind, crossover clinical trial

Reiner M et al., J Int Med Res 12:102 (1984)

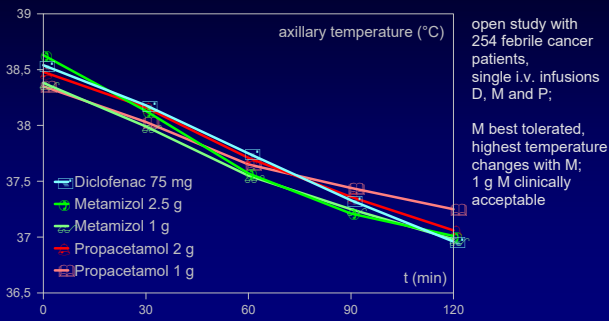


Metamizol versus paracetamol: a double-blind study in typhoid fever

Ajgaonkar VS et al., J Int Med Res 16:225 (1988)



Symptomatic intravenous antipyretic therapy: efficacy of metamizol, diclofenac, and propacetamol
 Oborilova A et al., J Pain Symptom Manage 24:608 (2002)

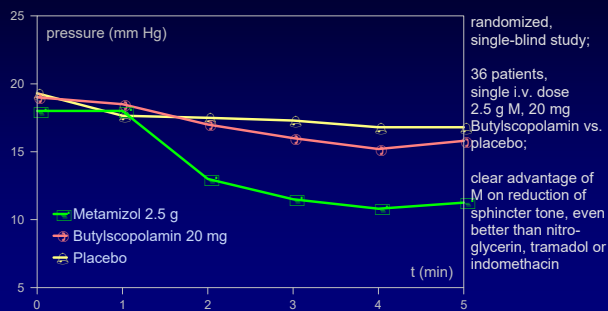


Qual der Wahl

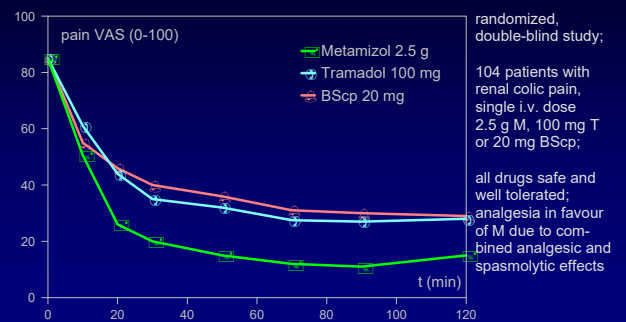


s.a. Edwards JE, Cochrane Library 3 (2003)

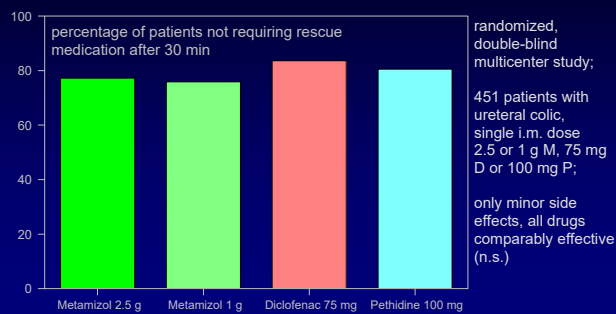
Spasmolytic effect of dipyrone on the motility of the sphincter of Oddi
 Brandstätter G et al., Internal Report Hoechst AG (1992)



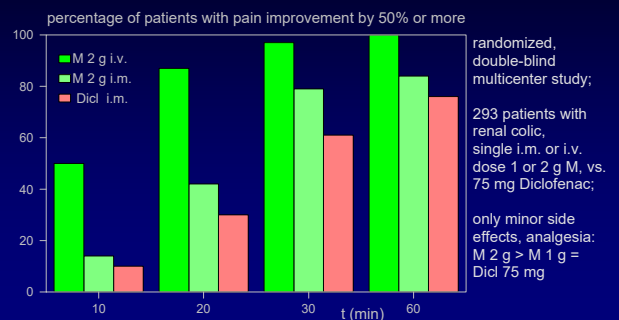
Double-blind study with dipyrone versus tramadol and butylscopolamine in acute renal colic pain
 Stankov G et al., World J Urol 12:155 (1994)



Comparative study of the efficacy of metamizol, diclofenac sodium and pethidine in acute renal colic
 Arnao JM et al., Eur J Clin Pharmacol 40:543 (1991)



Comparison of the onset and duration of the analgesic effect of metamizol in acute renal colic
 Muriel-Villoria C et al., Eur J Clin Pharmacol 48:103 (1995)

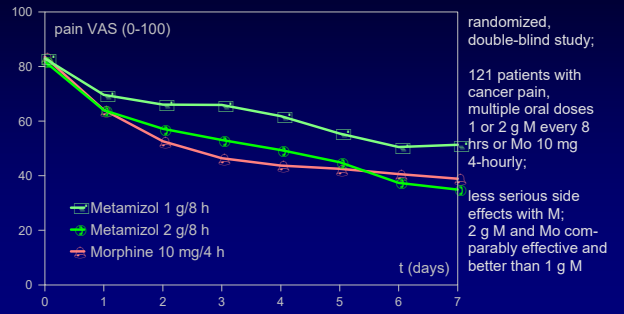


Qual der Wahl



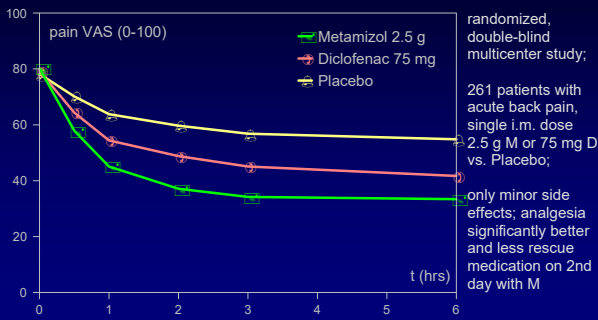
Efficacy and tolerance of oral metamizol versus oral morphine for cancer pain

Rodríguez M et al., Eur J Cancer 30:584 (1994)



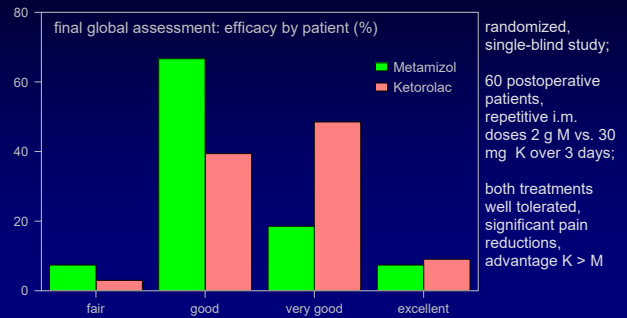
Parenteral metamizol versus diclofenac and placebo in patients with acute lumbago or sciatic pain

Babej-Dölle R et al., J Int Clin Pharmacol Ther 32:204 (1994)



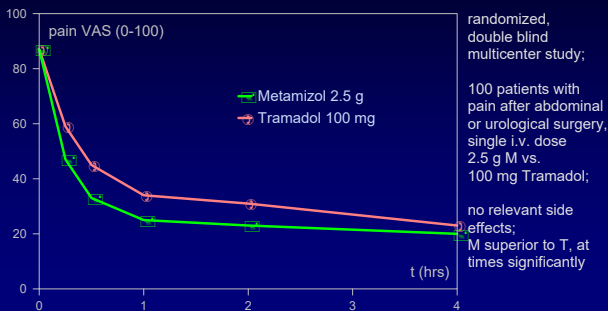
Ketorolac in a double-blind trial versus metamizol in orthopaedic surgery pain

Fernandez-Sabate A et al., Curr Ther Res 49:1016 (1991)



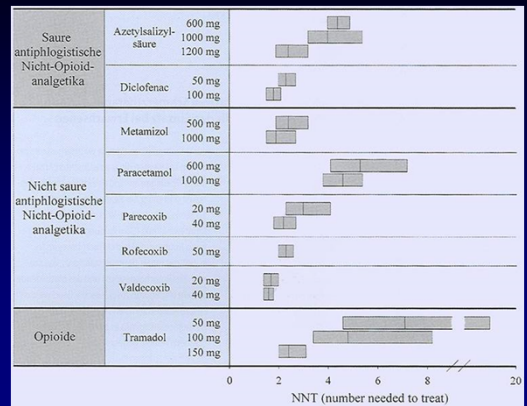
Controlled clinical trials of metamizol in postoperative pain conditions

Stankov G et al., Eur J Pain 16:56 (1995)

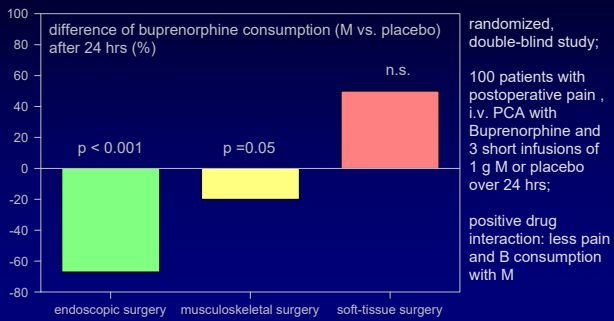


Non-opioid analgesics for perioperative pain therapy

Brack A et al., Anaesthesist 53:263 (2004)



Quantification of the analgesic efficacy of metamizol using patient-controlled analgesia
Steffen P et al., Anaesthesiol Intensivmed Notfallmed Schmerzther 31:143 (1996)

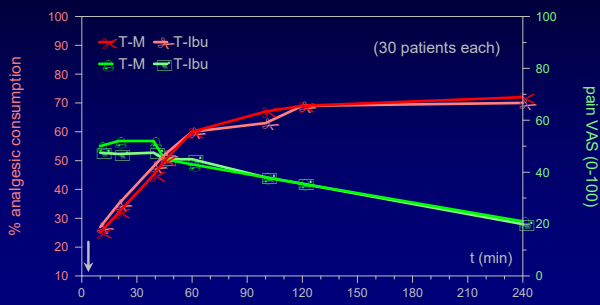


Metamizol-tramadol infusion for postoperative pain
Krimmer H et al., Chirurg 57:327 (1986)

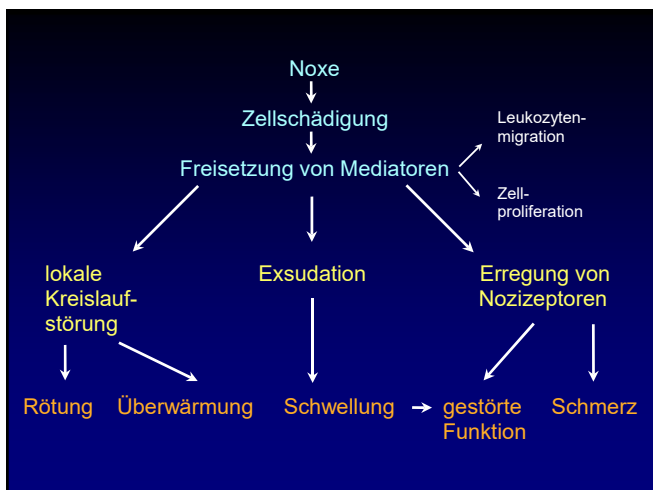
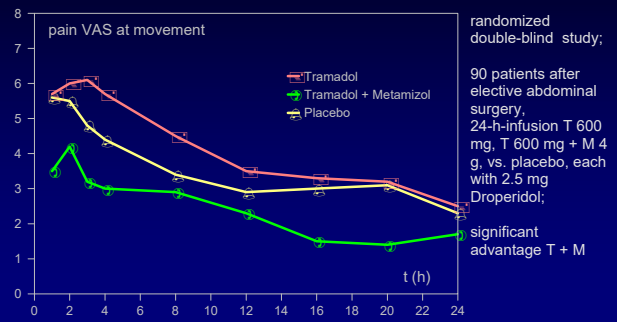
	mg / 500 ml
Tramadol	300-400
Metamizol	2500-5000
Haloperidol (for emesis only)	2

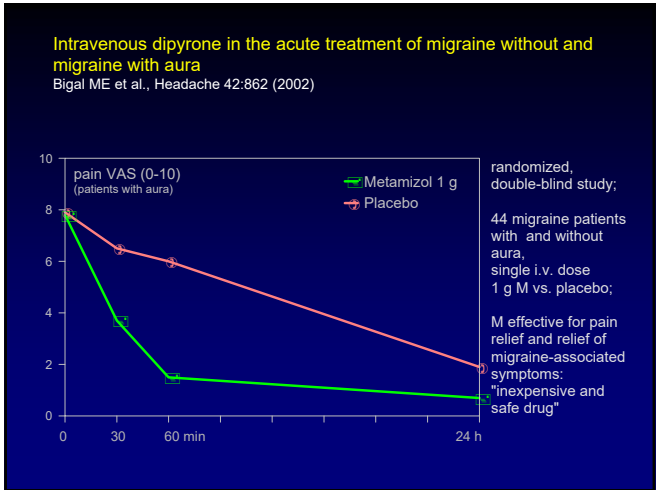
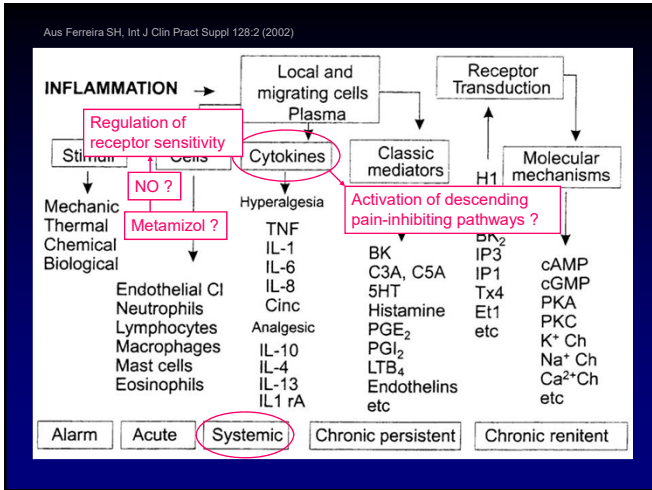
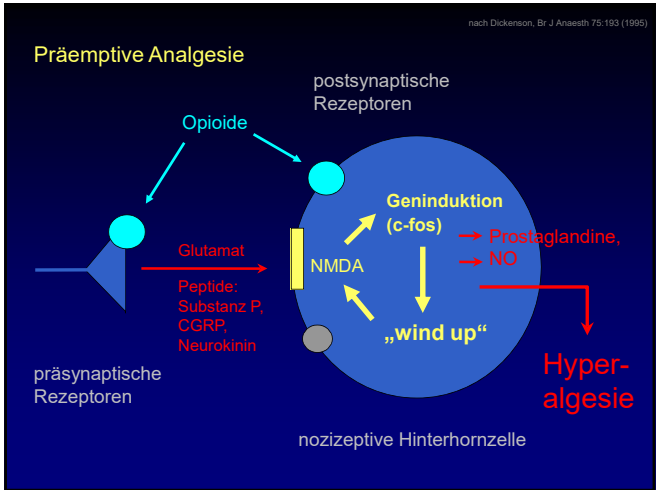
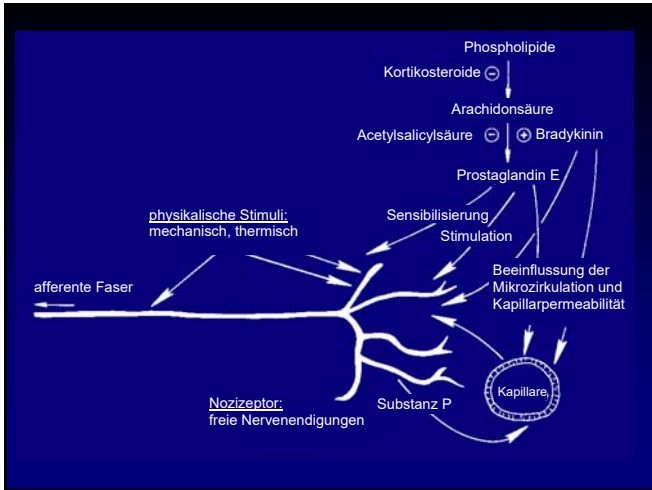
500 ml per 12-30 hrs, titrated to individual needs

Tramadol infusion in combination with i.v. metamizol or rectal ibuprofen for post-hysterectomy pain management
Striebel HW et al., Anaesthesist 41:354 (1992)



Superior postoperative analgesic efficacy of a continuous infusion of tramadol and dipyron (metamizol) versus tramadol alone
Spacek A et al., Acute Pain 5:3 (2003)





Fachinformationen
Aventis Pharma (2003)

Anwendungsgebiete

- akute starke Schmerzen nach Verletzungen oder Operationen,
- Koliken,
- Tumorschmerzen,
- sonstige akute oder chronische starke Schmerzen, soweit andere therapeutische Maßnahmen nicht indiziert sind,
- hohes Fieber, das auf andere Maßnahmen nicht anspricht.

Gegenanzeigen bei Patienten mit

- Allergie gegen Metamizol oder andere Pyrazolonderivate,
- Analgetika-Asthmasyndrom oder Analgetika-Intoleranz,
- akut-intermittierende Porphyrie,
- angeborener Glukose-6-Phosphat-Dehydrogenase-Mangel,
- Störung der Knochenmarksfunktion oder Erkrankungen des hämatopoetischen Systems;
- Säuglinge unter 3 Monaten oder unter 5 kg Körpergewicht.

Unerwünschte Wirkungen

Anaesthesist 2003; 52:321-325
DOI 10.1007/s00101-003-0455-5

Kasuistik

C. Janke¹ · J. Schmeck¹ · D. Passani¹ · P. Dodidou¹ · B. Stuck² · H. Kerger¹
¹ Institut für Anästhesiologie und Operative Intensivmedizin, Universitätsklinikum Mannheim, Fakultät für Klinische Medizin der Universität Heidelberg
² Hals-Nasen-Ohren-Klinik, Universitätsklinikum Mannheim, Fakultät für Klinische Medizin der Universität Heidelberg

Anaphylaktisches Herz-Kreislauf-Versagen nach intraoperativer Metamizolapplikation

Handbuch der unerwünschten Arzneimittelwirkungen: Metamizol
Müller-Oerlinghausen B et al. Urban & Fischer (1999)

Generalisierte Störungen

selten: schwere allergische Sofortreaktionen mit Schocksymptomatik; Metamizol p.o. 1:50.000, i.v. 1:5.000 (1:1.000 für Schockfragmente), Letalität bei Schock nach parenteraler Gabe ca. 25% !

Metamizol-Anwendungsbeschränkung vom Bundesgesundheitsamt:

1. kurzfristige Behandlung von schweren spastischen Schmerzzuständen (Gallen- und Nierensteinkoliken),
2. schwere akute Schmerzzustände, sofern andere Schmerzmittel kontraindiziert sind,
3. schwere Fieberzustände, die auf andere Maßnahmen nicht ansprechen,
4. Behandlung von Tumorschmerzen;
5. Injektionen sind nur erlaubt, wenn eine orale Gabe nicht in Frage kommt und die Voraussetzungen für eine Schockbehandlung gegeben sind.

Handbuch der unerwünschten Arzneimittelwirkungen: Metamizol
Müller-Oerlinghausen B et al. Urban & Fischer (1999)

Blut: Erhöhung der Blutungsneigung (Inhibition der Prostaglandinsynthese)

Haut: Hautrötung, Jucken, epidermale Nekrolyse, Exantheme, Lyell-Syndrom, Stevens-Johnson-Syndrom, angioneurotische Ödeme ...

Herz-Kreislauf-System: häufig Blutdruckabfall parallel zur Temperatursenkung (bei Antipyrese), cave alte Patienten, cave schnelle i.v. Injektion (myotrope spasmolytische Wirkung); Herzrhythmusstörungen bis hin zum AV-Block, insbesondere Tachykardie

Niere und Harnwege: Analgetikanephropathie eher bei Kombinationspräparaten; akutes Nierenversagen

Respirationstrakt: selten Asthma bronchiale

Verdauungssystem: häufig unspezifische gastrointestinale Beschwerden, Durchfälle, chronische Gastritis, Erbrechen, Stomatitis

Handbuch der unerwünschten Arzneimittelwirkungen: Metamizol
Müller-Oerlinghausen B et al. Urban & Fischer (1999)

Niere

Eine Sonderform der Niereninsuffizienz ist die **Analgetikanephropathie** mit chronisch interstitieller Nephritis und Papillenspitzennekrose. Sie wird besonders nach langjähriger Einnahme von analgetischen Kombinationspräparaten beobachtet (Kombination von renaler Minderdurchblutung und toxischen Metaboliten, insbesondere bei Kombinationspräparaten).

15% der chronischen Dialysepatienten haben eine solche Nephropathie. Begünstigend soll die Einnahme von Kombinationspräparaten sein, ohne dass die Tagesdosen exzessiv hoch sein müssen (3-5 Tbl. als Schwellendosis). **Direkte Beweise für einen kausalen Zusammenhang fehlen.**

Ebenso sind **akute Nierenversagen** beschrieben worden sowie, als Ausdruck der Nierenschädigung, **Gesichtsödeme** und **Ausscheidung pathologischer Harnbestandteile.**

Berrutti V et al., Nephrol Dial Transplant 13:2110 (1998)
Metamizol and acute interstitial nephritis (Case report of 30 g M po within 2 days)

Handbuch der unerwünschten Arzneimittelwirkungen: Metamizol
Müller-Oerlinghausen B et al. Urban & Fischer (1999)

Blut

selten: Leukozytopenie bzw. **Agranulozytose**, evtl. auch als Panzytopenie oder isolierte Anämie, meist nach 1-2 Wochen, Zeitraum aber sehr variabel.

Agranulozytose beginnend mit nekrotisierender Angina, Fieber- und Schleimhautulcerationen im Mund- und Rachenbereich, aplastische Anämien möglich.

Mechanismus: immunologisch; ansteigendes Gefährdungspotential bei Dosiserhöhung und längerer Dauer der Verabreichung, Häufigkeit 1:100.000 – 1 Mio.; möglicherweise auch höhere Inzidenzen.

Tödlicher Ausgang bei 5-25% (höchste Mortalität: therapieresistente Sepsis). Rechtzeitige Erkennung und Behandlung entscheidend für den Ausgang ! Keinesfalls Reexposition sowie Vermeidung anderer potentiell markschädigender Substanzen.

Arzneimittelinduzierte Agranulozytose
Heimpel H, Arzneimitteltherapie 12:101 (1994)

1990-1994 Bangkok, Thailand: Inzidenz 0,8; keine Todesfälle (Shapiro S et al. Am J Trop Med Hyg 60:573 (1999))
1987-1990 Niederlande: Inzidenz 1,6-2,2; keine Todesfälle (van der Klauw MM et al., Arch Intern Med 159:369 (1999))
1997-2001 Polen: Inzidenz 0,2; 1 Todesfall (Maj S, Lis V, J Int Med Res 30:488-95 (2002))
2002-2003 Polen: Inzidenz 0 (Maj S, Centkowski P, Med Sci Monit 10:PI93-95 (2004))

Inzidenz der Agranulozytose	Region	Fälle/Mio. Einwohner/Jahr	Todesfälle/Mio. Einwohner/Jahr
1967-1968	Finnland	10	?
1966-1970	Schweden	2,5	0,8
1966-1975	Schweden	2,6	0,8
1973-1978	Stockholm	9	1
1958-1984	Dänemark	?	0,4
1980-1984	verschiedene *	6,2	0,5
1980-1985	USA	7,2	?

* International Agranulocytosis and Aplastic Anemia Study, JAMA 256:1749 (1986) (Israel, Italien, Ungarn, Spanien, Schweden, Deutschland)

Kritik an IAAAS: Jahresinzidenz 1:20.000 wurde auf Wocheninzidenz 1:1 Mio heruntergerechnet (Wille H, Schönhöfer PS, Internist 43:469 (2002))

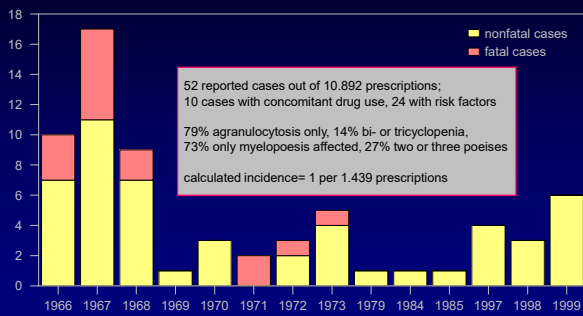
Arzneimittelinduzierte Agranulozytose
Heimpel H, Arzneimitteltherapie 12:101 (1994)

Schätzung des Agranulozytoserisikos für einzelne Arzneimittel. Je nach Angaben in den zugrundeliegenden Arbeiten wurde Dosis und Dauer einer "typischen" Behandlung oder ein Behandlungsjahr zugrunde gelegt.

Arzneimittel	Fälle/Mio. Exponierte
Clozapin (Neuroleptikum)	5.000
Dapson (Sulfonamid)	200-4.200
Levamisol (Immunmodulator)	11.000-80.000
Metamizol	1,1-330
Phenothiazine	830
Procainamid	44.000-55.700
Sulfasalazin (Chemotherapeutikum)	570
Thyreostatika	80-27.000

Agranulocytosis and other blood dyscrasias associated with dipyrone (metamizol)

Hedenmalm K, Spigset O, Eur J Clin Pharmacol 58:265 (2002)



Agranulocytosis associated with dipyrone (metamizol)

Ibanez L et al., Eur J Clin Pharmacol 60:821 (2004)

Retrospective analysis from Spanish Haematology Units (78 · 10⁶ person years):

273 community cases of agranulocytosis found, compared with 586 matched controls → incidence 5.2 cases per million inhabitants per year, 15 died;

among them 41 cases after metamizol use, 1 (34%) to > 21 days (5%), 4 of them with concomitant risky medication (thiamazole, butylpyrazolidines, erythromycin, spironolactone) → incidence 0.56 cases per million inhabitants per year, no casualties.

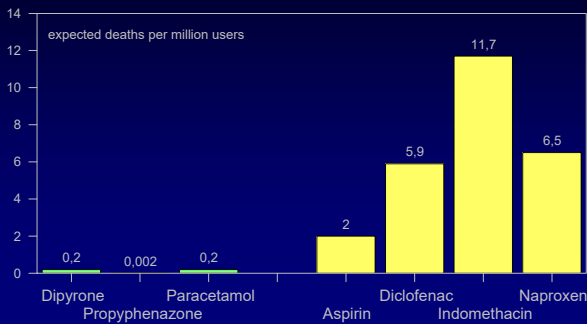
The risk disappeared after > 10 days since the last dose of metamizol, and it increased with duration of use.

In the Swedish study, duration of use was > 21 days in 66% of the patients, with a median cumulative dose of 100 g, intake of concomitant drugs was much higher.

The adverse public health impact from short-term use of non-narcotic analgesics and NSAIDs from an epidemiologic perspective

Martinez C; Klin Pharmakol Akt 7:38 (1996);

Andrade SE et al., J Clin Epidemiol 51:1357 (1998)



The adverse public health impact from short-term use of non-narcotic analgesics and NSAIDs from an epidemiologic perspective

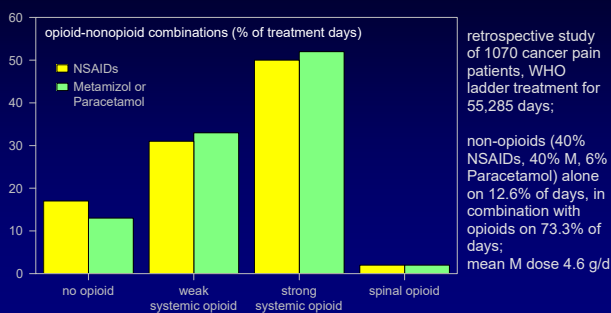
Martinez C; Klin Pharmakol Akt 7:38 (1996);

Andrade SE et al., J Clin Epidemiol 51:1357 (1998)

expected deaths per million users	GI Bleeding	Anaphylaxis	Aplastic Anemia	Agranulocytosis
Dipyrone	0,171	0,002	0	0,074
Proyphenazone	0	0,001	0	0,001
Paracetamol	0,19	0,001	0,006	0,001
Aspirin	2,018	0,002	0,003	0,006
Diclofenac	5,857	0,004	0,054	0
Indomethacin	11,576		0,12	0,035
Naproxen	6,474	0,002		

The importance on non-opioid analgesics for cancer pain relief according to the guidelines of the WHO

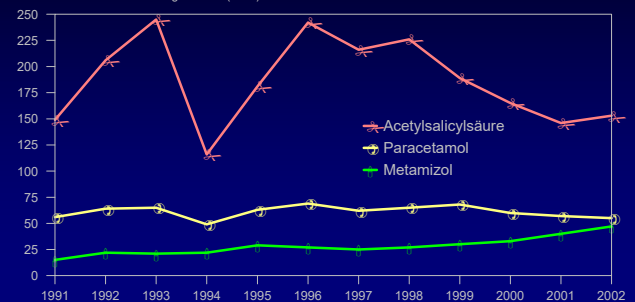
Grond S et al., Int J Clin Pharm Res 11:253 (1991)



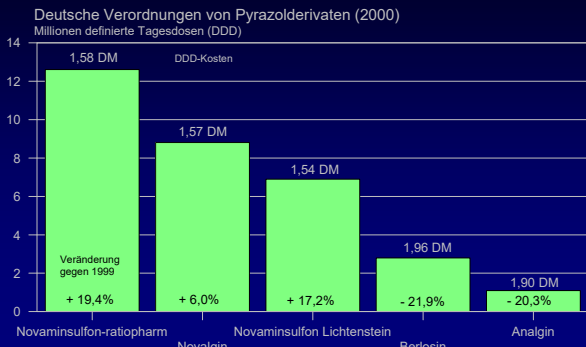
retrospective study of 1070 cancer pain patients, WHO ladder treatment for 55,285 days;
non-opioids (40% NSAIDs, 40% M, 6% Paracetamol) alone on 12.6% of days, in combination with opioids on 73.3% of days; mean M dose 4.6 g/d

Arzneimittelverordnungs-Report 2003: Analgetika

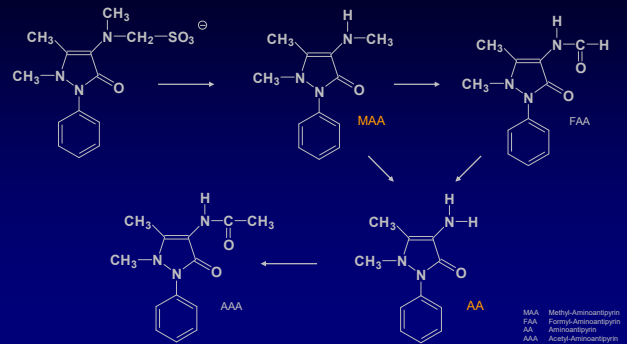
Deutsche Verordnungen
Millionen definierte Tagesdosen (DDD)



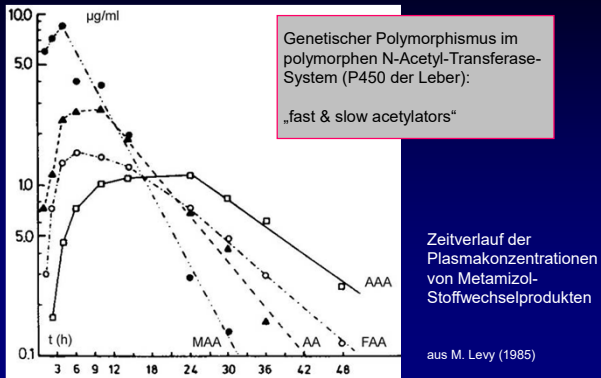
Arzneimittelverordnungs-Report 2001: Analgetika



Metamizol-Metabolismus

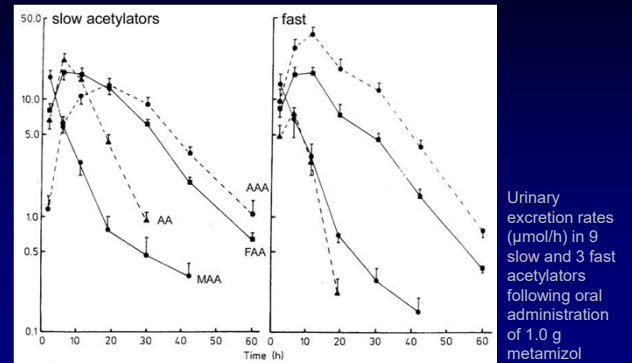


Metamizol-Metabolismus



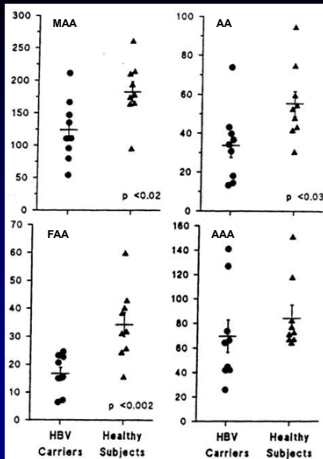
Formation and excretion of dipyrone metabolites in man

Zylber-Katz E et al., Eur J Clin Pharmacol 42:187 (1992)



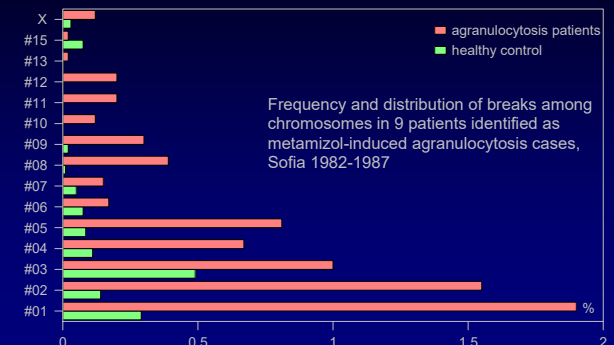
Impairment of the metabolism of dipyrone in asymptomatic carriers of the hepatitis B virus

Levy M et al., Clin Pharmacol Ther 62:6 (1997)



Genetic factors and risk of agranulocytosis from metamizol

Vlahov V et al., Pharmacogenetics 6:67 (1996)



Weitere Hinweise auf genetisch-bedingte Prädisposition zur Entwicklung einer Metamizol-bedingten Agranulozytose

Salama A, Schütz B, Kiefel V, Breithaupt H, Mueller-Eckhardt C (1989) Immune-mediated agranulocytosis related to drugs and their metabolites: mode of sensitization and heterogeneity of antibodies. Br J Haematol 72:127-32

Utrecht JP (1989) Idiosyncratic drug reactions: possible role of reactive metabolites generated by leukocytes. Pharm Res 6:265-73

Levy M (1997) Role of viral infections in the induction of adverse drug reactions. Drug Saf 16:1-8

Kowalski ML, Woszczyk G, Bienkiewicz B, Mis M (1998) Association of pyrazolone drug hypersensitivity with HLA-DQ and DR antigens. Clin Exp Allergy 28:1153-58

Herdeg C, Hilt F, Büchtemann A, Bianchi L, Klein R (2002) Allergic cholestatic hepatitis and exanthema induced by metamizole: verification by lymphocyte transformation test. Liver 22:507-13

Metamizol und Agranulozytose (1)

Effect of metamizol on promyelocytic and terminally differentiated granulocytic cells: comparative analysis with acetylsalicylic acid and diclofenac

García-Martínez JM et al., Biochem Pharmacol 65:209 (2003)

The results demonstrate that metamizol, MAA, ASA, and diclofenac, even at high pharmacological concentrations, neither affect the granulocytic differentiation process nor induce relevant apoptosis on terminally differentiated granulocytes. ...

These results also indirectly support that the mechanism of metamizol-induced agranulocytosis should be of immunoallergic origin since a toxic effect of this drug is excluded.

Metamizol und Agranulozytose (2)

Metamizole use by Latino immigrants: a common and potentially harmful home remedy

Bonkowsky TL et al., Pediatrics 109:1166 (2002)

A 4-year-old boy presented with fever, septic arthritis, and persistent neutropenia. Bone marrow biopsy revealed no evidence of neoplasia. The boy had been given metamizole for pain before onset of his illness. Additional inquiry revealed that the patient's mother was hospitalized previously for overwhelming sepsis associated with metamizole use. It was found that 35% of Spanish-speaking Latino families had used metamizole; 25% of these families had purchased the medication in the United States.

Physicians must be aware of the availability and use in specific patients populations and its potential for harmful side effects.

Metamizol und Agranulozytose (3)

Behandlung einer medikamenten-induzierten Agranulozytose mit Granulozyten-Colony Stimulating Factor (G-CSF) auf einer operativen Intensivstation

Huss B et al., Anaesthesiol Intensivmed Notfallmed Schmerzther 31:529 (1996)

Aufgrund wiederholter Metamizol-Gaben (12,5 g in 9 Tagen) entwickelte ein 41-jähriger Patient mit schwerem Schädel-Hirn-Trauma und Sepsis eine medikamenteninduzierte Agranulozytose. Durch frühzeitige Therapie mit G-CSF (Neupogen®), 5 µg/kg s.c., konnte die neutropenische Phase auf 4 Tage begrenzt werden.

Absetzen des auslösenden Medikamentes, strikte Vermeidung der Reexposition, sowie hochdosierte Behandlung mit bakteriziden Breitbandantibiotika sind Therapie-Standards.

Metamizol und Agranulozytose (4)

Drug-induced agranulocytosis: clinical study of 19 cases

Márquez JA et al., Sangre 43:436 (1998)

From January 1991 to June 1996 we diagnosed 19 cases of agranulocytosis with drugs at our Spanish hospital (incidence rate 9.4 per million inhabitants per year). The drugs most commonly involved were metamizol (5 cases) and ticlopidine (4), diclofenac had been used in 1 patient.

In 15 patients fever blew up, and 16 presented some infectious location. Granulocyte-colony stimulating factor (G-CSF) was used in 13 patients, observing a significantly quicker haematological recovery (5.7 days vs. 9.1).

Mortality was 0 %.

* Thrombozytenaggregationshemmer

Metamizol und Agranulozytose (5)

Agranulocytosis due to metamizole. Anesthetic approach

Álvarez MPP et al., Rev Esp Anesthesiol Reanim 45:248 (1998)

A 85-year-old man came to the emergency room with a femoral fracture. He received 1 g metamizole i.v. every 8 hours for analgesia. 10 hours after admission a routine blood cell count showed a rapid fall in the number of leucocytes: at 24 hours the count was 600·10⁹/l.

Postponement of surgery was advisable and treatment with granulocyte-colony stimulating factor (G-CSF), 5 µg/kg/d was initiated. Agranulocytosis resolved after 3 days of treatment, after which time surgery was performed under subarachnoid anesthesia. 2 packs of red blood cells were required during the immediate postoperative period.

12 days after surgery the patient was released.

Metamizol und Agranulozytose (6)

Hematopoietic growth factors in drug-induced agranulocytosis

Pavithran K, Thomas M, J Assoc Physicians India 50:679 (2002)

We report 9 cases of drug-induced agranulocytosis (1 metamizol, 1 ibuprofen) treated with granulocyte macrophage-colony stimulating factor (GM-CSF) in a dose of 300 µg/d s.c. All patients had evidence of systemic infection. Mean time to reach an absolute neutrophil count of $0.5 \cdot 10^9/l$ was 3 days. One patient (dapson) succumbed to the disease after multiorgan failure.

No adverse events were observed with GM-CSF.

We conclude that hematopoietic growth factors are useful in shortening the period of neutropenia and reducing morbidity and mortality in these patients.

Metamizol und Agranulozytose (7)

To use or not to use dipyrone? Or maybe, central station versus ER?

That is the question...

Bensenor I, Sao Paulo Med J 119:190 (2001)

Although the evidence for possible serious side effects from dipyrone use are weak, a strong lobby against its prescription was launched in the Brazil lay press.

The Brazilian Public Health Surveillance System organized a panel with the participation of many Brazilian and international scientists. It was concluded, based on the evidence available up to the present day, that the sale of dipyrone as an over-the-counter medication in Brazil could continue. In our opinion, this was the correct decision.

Metamizol und Agranulozytose (8)

To use or not to use dipyrone? Or maybe, central station versus ER?

That is the question...

Bensenor I, Sao Paulo Med J 119:190 (2001)

There are rumours that there was a potential conflict of interest in the American prohibition of dipyrone, considering that it was a German-developed drug. The rational is weak, but the emotion is strong.

In the light of evidence-based medicine and forgetting emergency room episodes:

It is time to take decisions based on evidence and not on prejudices.

Literatur-Splitter (1)

In der klinischen Praxis könnte eine Schmerztherapie nach endoskopischen Eingriffen folgendermaßen aussehen:

1. Präoperative Gabe von **1 g Metamizol i.v.** über 15 min vor oder nach der Narkoseeinleitung.
2. Repetition von **1 g Metamizol in 6- bis 8-stündigen Abständen** i.v. oder alternativ oral.
3. Supplementierung dieser Basisanalgesie mit einem Opioid (z.B. Piritramid, Buprenorphin, Tramadol).

Steffen P et al., Chirurg 68:806 (1997)

Literatur-Splitter (2)

In 120 ambulatory patients undergoing hand surgery under i.v. regional anesthesia, oral tablets were prescribed at discharge (tramadol 100 mg, **metamizol 1 g** or paracetamol 1 g, each to be applied **every 6 hours**). No drug alone produced effective analgesia in all patients. Tramadol was the most effective (in 23% rescue doses required), but with the highest incidence of side effects. Metamizol (31% rescue) and paracetamol (42%) provided good analgesia and a small incidence of side effects.

Rawal N et al., Anesth Analg 92:347 (2001)

Literatur-Splitter (3)

The use of continuous epidural infusion of lidocaine and fentanyl, in combination with **iv metamizol (40 mg/kg)** provided slightly better pain control than our usual regimen of epidural morphine, also in combination with **iv metamizol (40 mg/kg)** during the first three postoperative days in healthy children (2-16 yr of age) undergoing orthopedic surgery without increasing the incidence of adverse side-effects or systemic toxicity.

Reinoso-Barbero F et al., Can J Anesth 49:67 (2002)

Literatur-Splitter ⁽⁴⁾

Postoperative pain in 93 patients after plug-and-patch repair of recurrent inguinal hernia decreased continuously from the morning of the first postoperative day (VAS: 5.4) until day 13 (VAS <1). The median amount of analgesics given to the patients for 4 days was **dipyron 5.2 g (range 2.1-8.4)**. Median duration of hospital stay was 5 days, limitation to daily activity 6 days, and 34 patients who were employed had returned to work after 21 days.

Zieren J et al., Eur J Surg 168:18-21 (2002)