Hépatites médicamenteuses: diagnostic et hépatites au paracétamol

5e journée régionale de pharmacovigilance

8 octobre 2015

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Service des maladies de l'appareil digestif

CHRU de Lille

Hépatites médicamenteuses: généralités

Introduction: l'hépatotoxicité

- Fréquence mal connue
- Médicament souvent retiré du marché si prévalence >1%
- Risque global estimé à 1/10.000-100.000
- Importance de la pharmacovigilance (essais de phase III)
- Champion toutes catégories: paracétamol

Larrey Gastroenterol Clin Biol 2009

Hépatite aiguë

	Drug		Viral			Unknown	Other
	Paracetamol	Non-paracetamol	HAV	HBV	HEV		
Spain 1992–2000[18]	2%	17%	2%	32%	--	35%	12%
Sweden 1994–2003[19]	42%	15%	3%	4%	--	11%	25%
UK 1999–2008[20]	57%	11%	2%	5%	1%	17%	7%
Germany 1996–2005[21]	15%	14%	4%	18%	--	21%	28%
USA 1998–2001[22]	39%	13%	4%	7%	--	18%	19%
Australia 1988–2001[23]	36%	6%	4%	10%	--	34%	10%
Pakistan 2003–05[24]	0%	2%	7%	20%	60%	7%	4%
India 1989–96[25]	0%	1%	2%	15%	44%	31%	7%
Sudan 2003–04[26]	0%	8%	0%	22%	5%	38%	27%

--=not reported. HAV=hepatitis A virus. HBV=hepatitis B virus. HEV=hepatitis E virus.

Table 2: **Selected reports of causes of acute liver failure**

Bernal et al. Lancet 2010

Hépatites médicamenteuses

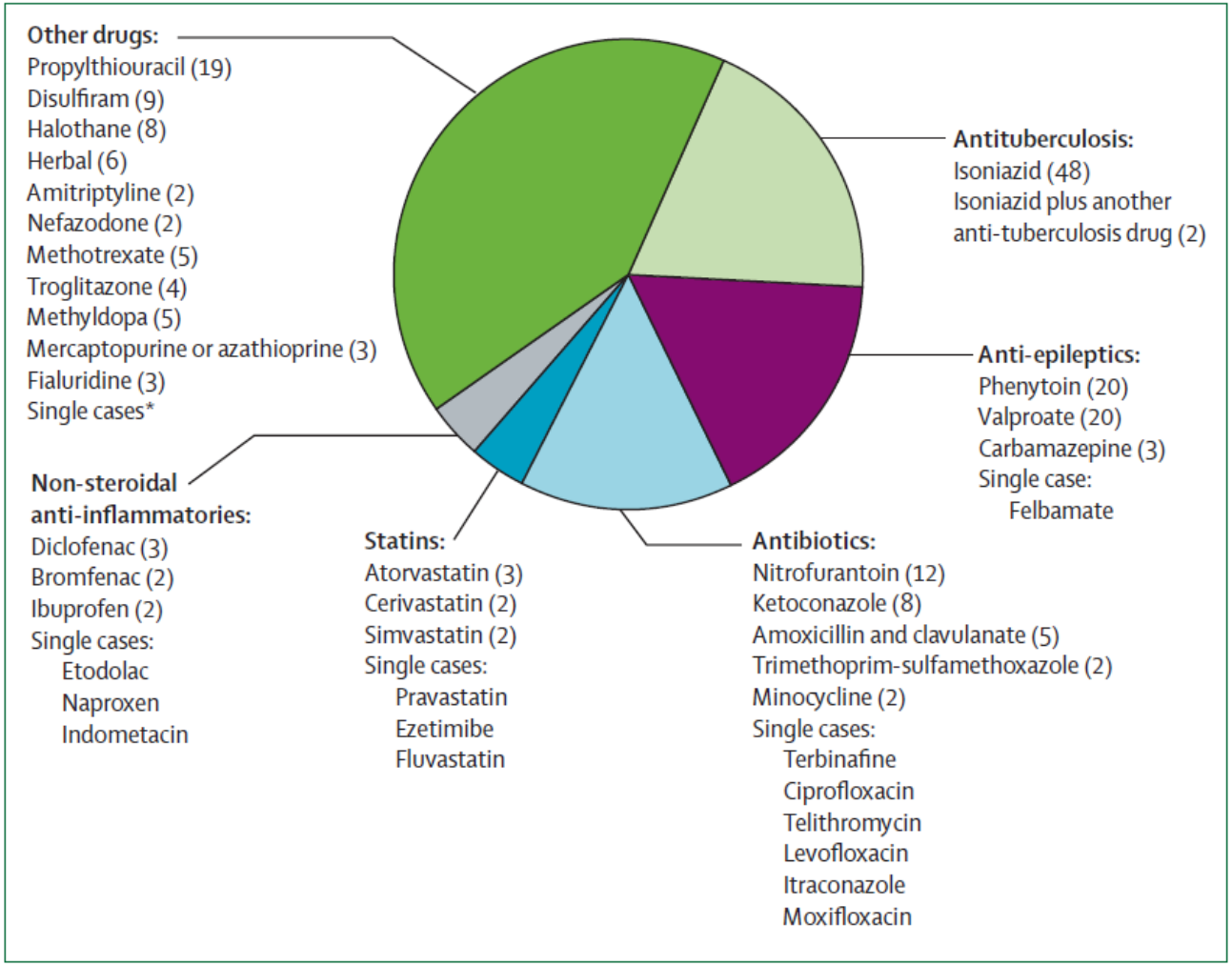

Figure 2: **Non-paracetamol-based drugs causing acute liver failure in patients requiring emergency liver transplantation in USA, 1987–2006**

Bernal et al. Lancet 2010

Diagnostic biologique

ALAT > 3N

Hepatocellular (Elevated ALT)	Mixed (Elevated ALP + Elevated ALT)	Cholestatic (Elevated ALP + TBL)
Acarbose	Amitriptyline	Amoxicillin–clavulanic acid
Acetaminophen	Azathioprine	Anabolic steroids
Allopurinol	Captopril	Chlorpromazine
Amiodarone	Carbamazepine	Clopidogrel
Baclofen	Clindamycin	Oral contraceptives
Buproprion	Cyproheptadine	Erythromycins
Fluoxetine	Enalapril	Estrogens
HAART drugs	Flutamide	Irbesartan
Herbals: kava kava and germander	Nitrofurantoin	Mirtazapine
	Phenobarbital	Phenothiazines
Isoniazid	Phenytoin	Terbinafine
Ketoconazole	Sulfonamides	Tricyclics
Lisinopril	Trazodone	
Losartan	Trimethoprim–sulfamethoxazole	
Methotrexate	Verapamil	
NSAIDs		
Omeprazole		
Paroxetine		
Pyrazinamide		
Rifampin		
Risperidone		
Sertraline		
Statins		
Tetracyclines		
Trazodone		
Trovafloxacin		
Valproic acid		

Critère d'alarme: ictère

PAL > 2N

Navarro and Senior N Engl J Med 2006

Diagnostic biologique

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Herbals: kava kava and germander	Nitrofurantoin	Mirtazapine
Isoniazid	Phenobarbital	Phenothiazines
Ketoconazole	Phenytoin	Terbinafine
Lisinopril	Sulfonamides	Tricyclics
Losartan	Trazodone	
Methotrexate	Trimethoprim–sulfamethoxazole	
NSAIDs	Verapamil	
Omeprazole		
Paroxetine		
Pyrazinamide		
Rifampin		
Risperidone		
Sertraline		
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Critère d'alarme: ictère

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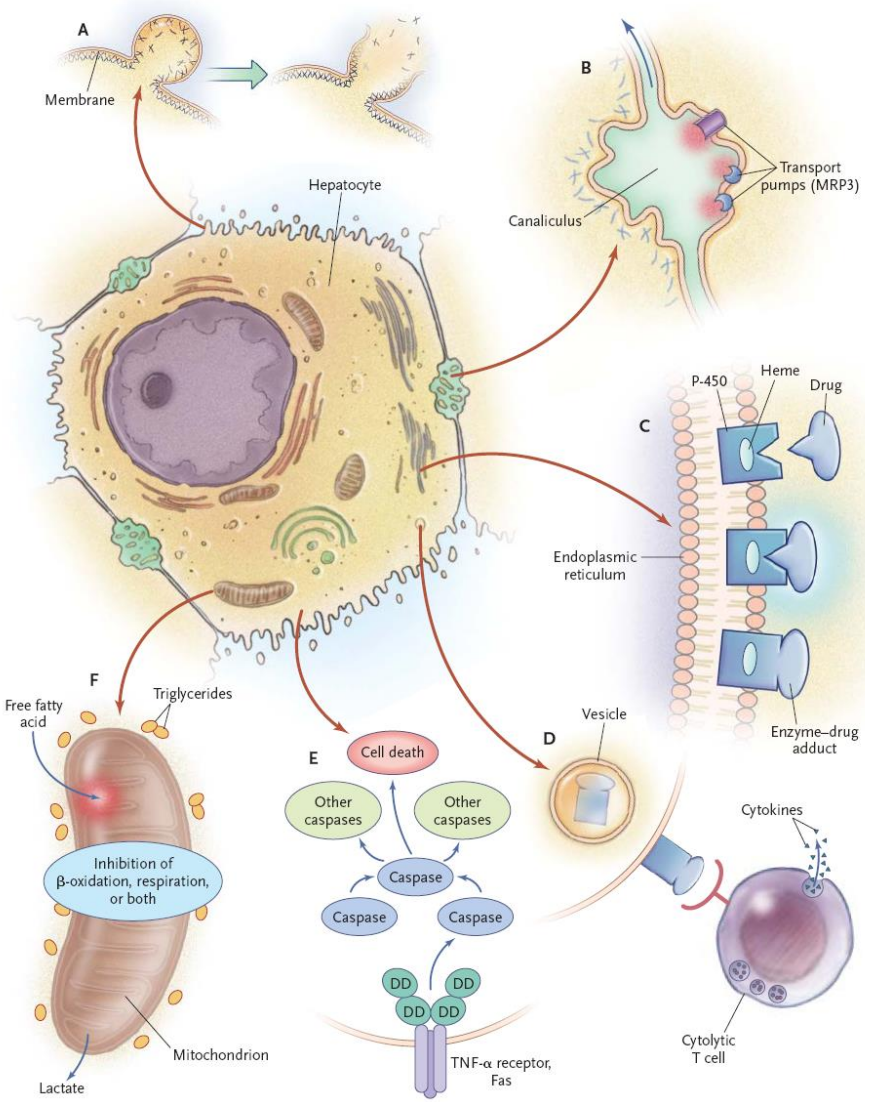
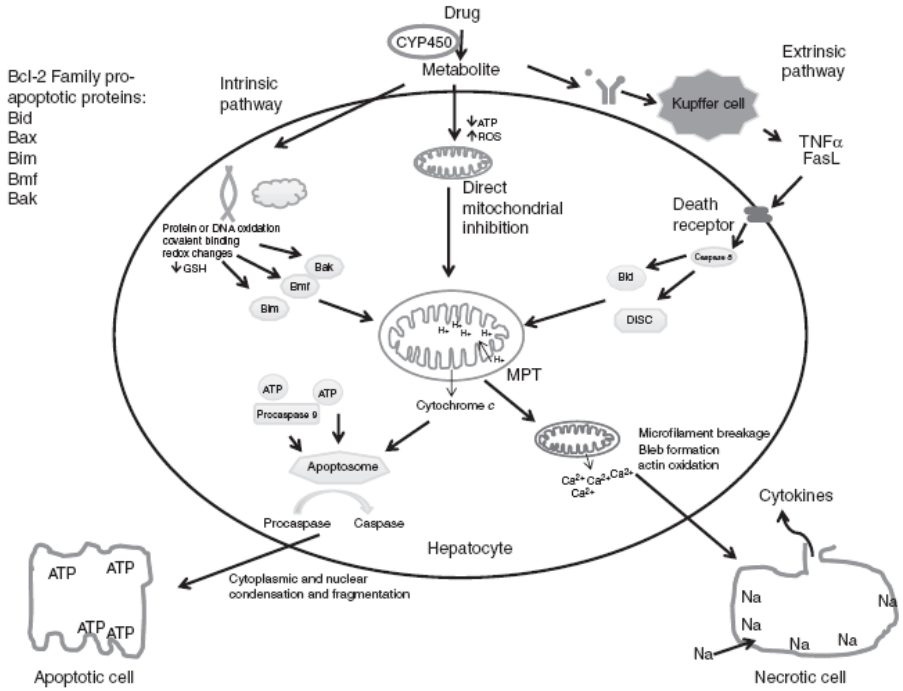
Navarro and Senior N Engl J Med 2006

Mécanismes de l'hépatotoxicité





Lee N Engl J Med 2003
Au et al. Aliment Pharmacol Ther 2011

Mécanismes de l'hépatotoxicité

- Hépatite toxique (surdosage): liée à une agression directe par la molécule ou ses métabolites

  Ex: paracétamol

- Hépatite idiosyncrasique (non toxique):
  - **Métabolique**: surtout cytolytique, non liée à l'immunité

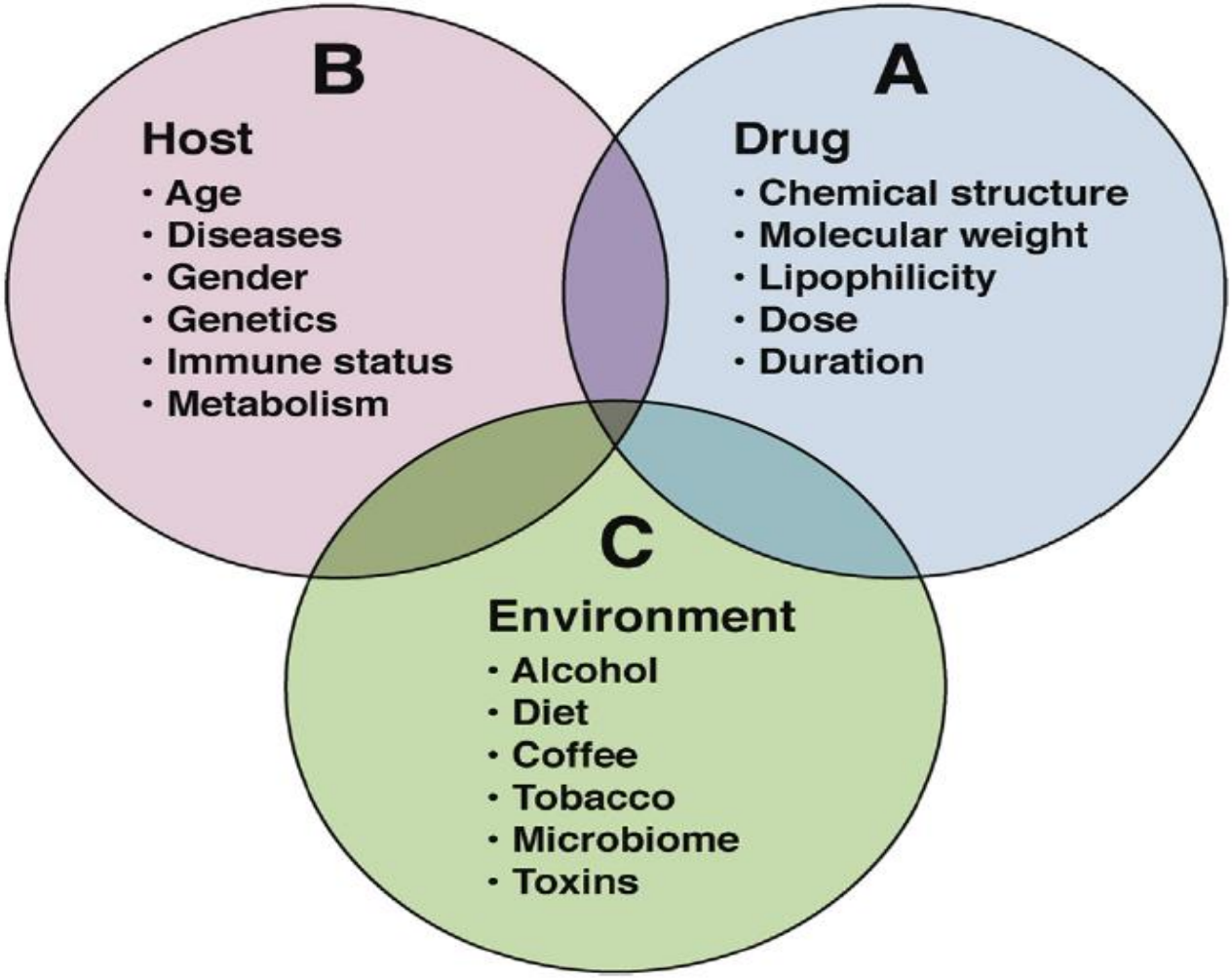
    Ex: isoniazide
  - **Immunoallergique**: liée à des néoantigènes, manifestations d'hypersensibilité (fièvre, PNE, éruption cutanée). Récidivent vite en cas de réintroduction du médicament.

    Ex: sulfaméthoxazole
  - **Auto-immune**: est une hépatite immuno-allergique avec formation d'auto-anticorps

    Ex: nitrofurantoïne

Larrey Gastroenterol Clin Biol 2009

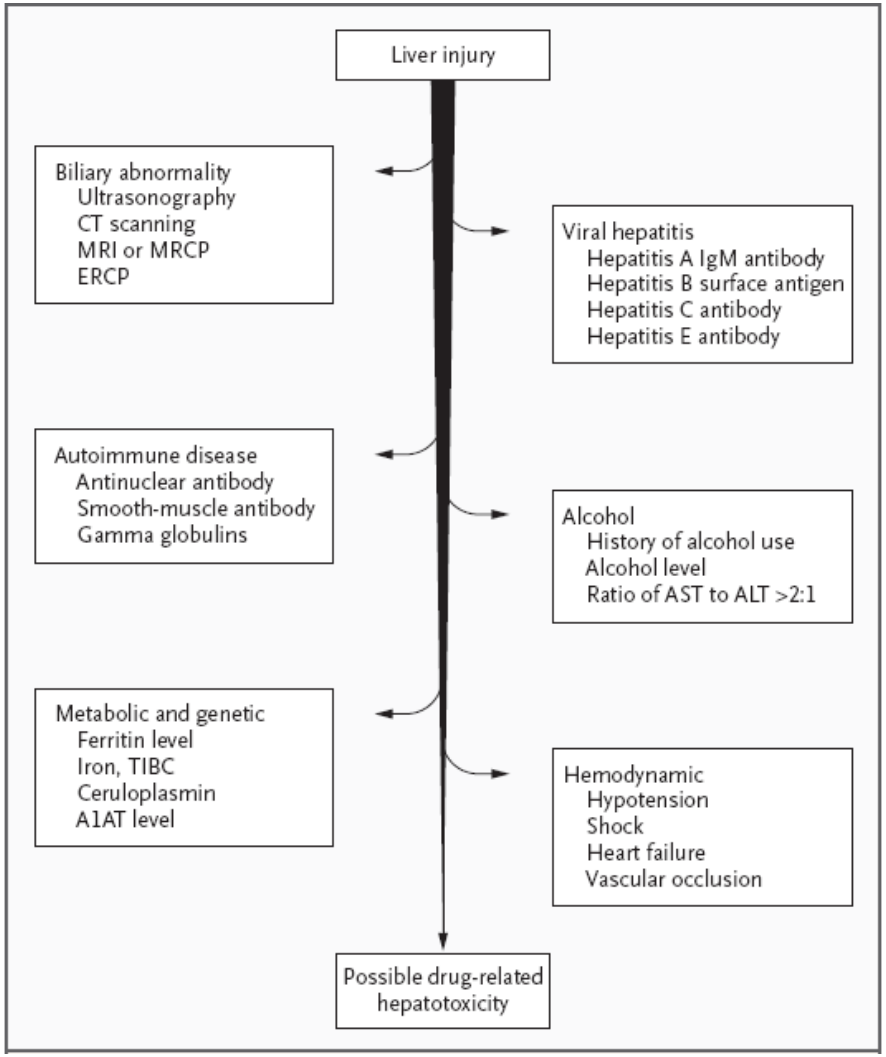
Réactions idiosyncrasiques



Fontana RJ. Gastroenterology 2014

Hépatites médicamenteuses: aspects pratiques

Démarche diagnostique



Navarro and Senior N Engl J Med 2006

Concept de la loi de Hy (Hy's law)

Hyman Zimmermann (années 1960):

- Gravité en cas d'hépatite cytolytique avec ictère (10% de mortalité)
- Attitude validée par la FDA (développement)
- Correspond à ALAT >3N et bilirubine >2N
- Alternative: **« R »**: ALAT/ PAL (en x N)
  - Cytolytique (hépatocellulaire si R>5)
  - Cholestatique si <2
  - Mixte entre les deux
- Bémol: spécificité mauvaise

Nouveau rapport « R » (nR)

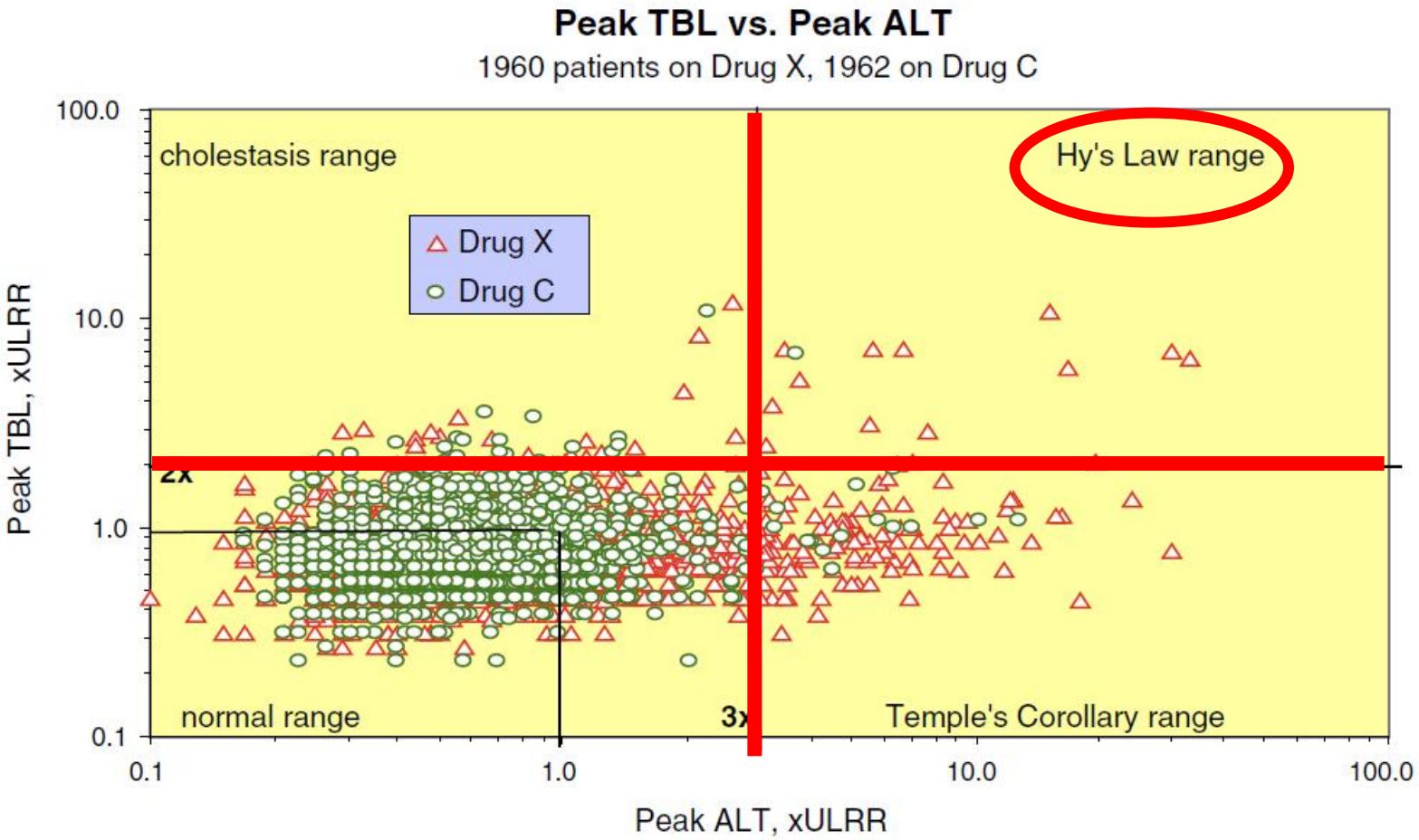
Amélioration de la spécificité de la loi de Hy

Bilirubine totale > 2 LSN
Et
“nR” ALAT ou ASAT (le plus élevé) LSN / phosphatases alcalines LSN > 5

	ALT > 3, TBL > 2		R ≥ 5, TBL > 2		nR[a] ≥ 5, TBL > 2	
	No ALF/OLT	ALF/OLT	No ALF/OLT	ALF/OLT	No ALF/OLT	ALF/OLT
At DILI recognition	318	27	250	25	255	27
Sensitivity	90%		83%		90%	
Specificity	44%		67%		63%	
LR+	1.6		2.51		2.43	
LR-	0.23		0.25		0.16	
At peak ALT level	308	28	252	23	255	25
Sensitivity	93%		79%		89%	
Specificity	43%		61%		62%	
LR+	1.63		2.02		2.34	
LR-	0.16		0.34		0.18	
At peak TBL level	367	23	231	18	248	18
Sensitivity	77%		72%		72%	
Specificity	49%		65%		65%	
LR+	1.5		2.05		2.05	
LR-	0.46		0.43		0.43	

Robles-Diaz M et al. Gastroenterology 2014

En pratique…



Ne conclut pas à l'hépatotoxicité! Identifie les sujets à étudier plus précisément

Senior et al. Drug Saf 2014

L’épineux problème du délai

- Considéré comme évocateur si entre 7 jours et 3 mois après le début du médicament
- Durée courte possible (24 à 48 heures) si exposition antérieure

- Imputabilité possible si diminution ≥50% des transaminases dans la semaine suivant l’arrêt

Imputabilité

RUCAM Causality Assessment

Drug: _____ Initial ALT: _____ Initial Alk P: _____ R ratio = [ALT/ULN] ÷ [Alk P/ULN] = _____ ÷ _____ = _____

The R ratio determines whether the injury is hepatocellular (R > 5.0), cholestatic (R < 2.0), or mixed (R = 2.0 – 5.0)

	Hepatocellular Type		Cholestatic or Mixed Type		Assessment
1. Time to onset					
	Initial Treatment	**Subsequent Treatment**	**Initial Treatment**	**Subsequent Treatment**	**Score** (check one only)
○ From the beginning of the drug:					
• Suggestive	5 – 90 days	1 – 15 days	5 – 90 days	1 – 90 days	☐ +2
• Compatible	< 5 or > 90 days	> 15 days	< 5 or > 90 days	> 90 days	☐ +1
○ From cessation of the drug:					
• Compatible	≤ 15 days	≤ 15 days	≤ 30 days	≤ 30 days	☐ +1
Note: If reaction begins before starting the medication or >15 days after stopping (hepatocellular), or >30 days after stopping (cholestatic), the injury shou be considered unrelated and the RUCAM cannot be calculated.					
2. Course	**Change in ALT between peak value and ULN**		**Change in Alk P (or total bilirubin) between peak value and ULN**		**Score** (check one only)
After stopping the drug:					
• Highly suggestive	Decrease ≥ 50% within 8 days		Not applicable		☐ +3
• Suggestive	Decrease ≥ 50% within 30 days		Decrease ≥ 50% within 180 days		☐ +2
• Compatible	Not applicable		Decrease < 50% within 180 days		☐ +1
• Inconclusive	No information or decrease ≥ 50% after 30 days		Persistence or increase or no information		☐ 0
• Against the role of the drug	Decrease < 50% after 30 days **OR** Recurrent increase		Not applicable		☐ -2
○ **If the drug is continued:**					
• Inconclusive	All situations		All situations		☐ 0
3. Risk Factors:	**Ethanol**		**Ethanol or Pregnancy (either)**		**Score** (check one for each)
○ Alcohol or Pregnancy	Presence		Presence		☐ +1
	Absence		Absence		☐ 0
○ Age	Age of the patient ≥ 55 years		Age of the patient ≥ 55 years		☐ +1
	Age of the patient < 55 years		Age of the patient < 55 years		☐ 0

RUCAM: Roussel-Uclaf Causality Assessment Method

4. Concomitant drug(s):	Score (check one only)
○ None or no information or concomitant drug with incompatible time to onset	☐ 0
○ Concomitant drug with suggestive or compatible time to onset	☐ -1
○ Concomitant drug known to be hepatoxic with a suggestive time to onset	☐ -2
○ Concomitant drug with clear evidence for its role (positive rechallenge or clear link to injury and typical signature)	☐ -3

5. Exclusion of other causes of liver injury:		Score (check one only)
Group I (6 causes): ○ **Acute viral hepatitis** due to **HAV** (IgM anti-HAV), or ○ **HBV** (HBsAg and/or IgM anti-HBc), or ○ **HCV** (anti HCV and/or HCV RNA with appropriate clinical history) ○ **Biliary obstruction** (By imaging) ○ **Alcoholism** (History of excessive intake and AST/ALT ≥ 2) ○ **Recent history of hypotension, shock or ischemia** (within 2 weeks of onset) **Group II (2 categories of causes):** ○ Complications of underlying disease(s) such as autoimmune hepatitis, sepsis, chronic hepatitis B or C, primary biliary cirrhosis or sclerosing cholangitis; or ○ Clinical features or serologic and virologic tests indicating acute CMV, EBV, or HSV.	○ All causes in Group I and II ruled out	☐ +2
	○ The 6 causes of Group I ruled out	☐ +1
	○ Five or 4 causes of Group I ruled out	☐ 0
	○ Less than 4 causes of Group 1 ruled out	☐ -2
	○ Non drug cause highly probable	☐ -3

6. Previous information on hepatotoxicity of the drug:	Score (check one only)
○ Reaction labeled in the product characteristics	☐ +2
○ Reaction published but unlabeled	☐ +1
○ Reaction unknown	☐ 0

7. Response to readministration:			Score (check one only)
○ Positive	Doubling of ALT with drug alone	Doubling of Alk P (or bilirubin) with drug alone	☐ +3
○ Compatible	Doubling of the ALT with the suspect drug combined with another drug which had been given at the time of onset of the initial injury	Doubling of the Alk P (or bilirubin) with the suspect drug combined with another drug which had been given at the time of onset of the initial injury	☐ +1
○ Negative	Increase of ALT but less than ULN with drug alone	Increase of Alk P (or bilirubin) but less than ULN with drug alone	☐ -2
○ Not done or not interpretable	Other situations	Other situations	☐ 0
		TOTAL (add the checked figures)	

Abbreviations used: ALT, alanine aminotransferase; Alk P, alkaline phosphatase; ULN, upper limit of the normal range of values
Modified from: Danan G and Benichou C. J Clin Epidemiol 1993; 46: 1323-30.

4. Concomitant drug(s):			Score (check one only)
○ None or no information or concomitant drug with incompatible time to onset			☐ 0
○ Concomitant drug with suggestive or compatible time to onset			☐ -1
○ Concomitant drug known to be hepatoxic with a suggestive time to onset			☐ -2
○ Concomitant drug with clear evidence for its role (positive rechallenge or clear link to injury and typical signature)			☐ -3

5. Exclusion of other causes of liver injury:			Score (check one only)
Group I (6 causes): ○ **Acute viral hepatitis** due to **HAV** (IgM anti-HAV), or ○ **HBV** (HBsAg and/or IgM anti-HBc), or ○ **HCV** (anti HCV and/or ○ **Biliary obstruction** (By in ○ **Alcoholism** (History of ex ○ **Recent history of hypote** **Group II (2 categories of cau** ○ Complications of underly B or C, primary biliary cir ○ Clinical features or serol		○ All causes in Group I and II ruled out ○ The 6 causes of Group I ruled out	☐ +2 ☐ +1 ☐ 0 ☐ -2 ☐ -3

6. Previous information on h			Score (check one only)
○ Reaction labeled in the p			☐ +2
○ Reaction published but u			☐ +1
○ Reaction unknown			☐ 0

7. Response to readministrat			Score (check one only)
○ Positive			☐ +3
○ Compatible		spect been	☐ +1
○ Negative		N with	☐ -2
○ Not done or not interpretable	Other situations	Other situations	☐ 0

TOTAL (add the checked figures)

0 ou moins = médicament “exclu”

1 à 2 = imputabilité peu probable

3 à 5 = “possible”

6 à 8 = “probable”;

>8 = “très probable” ou “certaine”

Abbreviations used: ALT, alanine aminotransferase; Alk P, alkaline phosphatase; ULN, upper limit of the normal range of values
Modified from: Danan G and Benichou C. J Clin Epidemiol 1993; 46: 1323-30.

Recommandations FDA

- Arrêt du traitement si:
  - ALAT ou ASAT > 8N
  - ALAT ou ASAT > 5N pdt > 2 sem
  - ALAT ou ASAT > 3N **et** (bili tot > 2N ou INR > 1,5)
  - ALAT ou ASAT > 3N avec symptômes (ex: fatigue, N&V, douleurs hépatiques, fièvre, rash) ou éosinophilie >5%

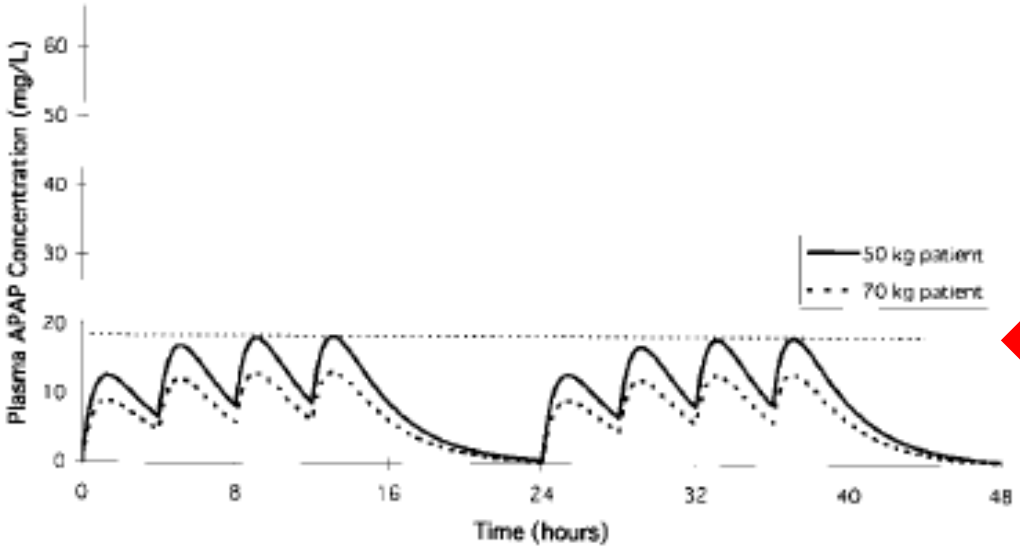
- Reprise du traitement : devrait généralement être évitée lorsque ALT/AST > 5N sauf s'il n'existe pas d'alternative thérapeutique et après information du patient

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Hépatite au paracétamol

Métabolisme

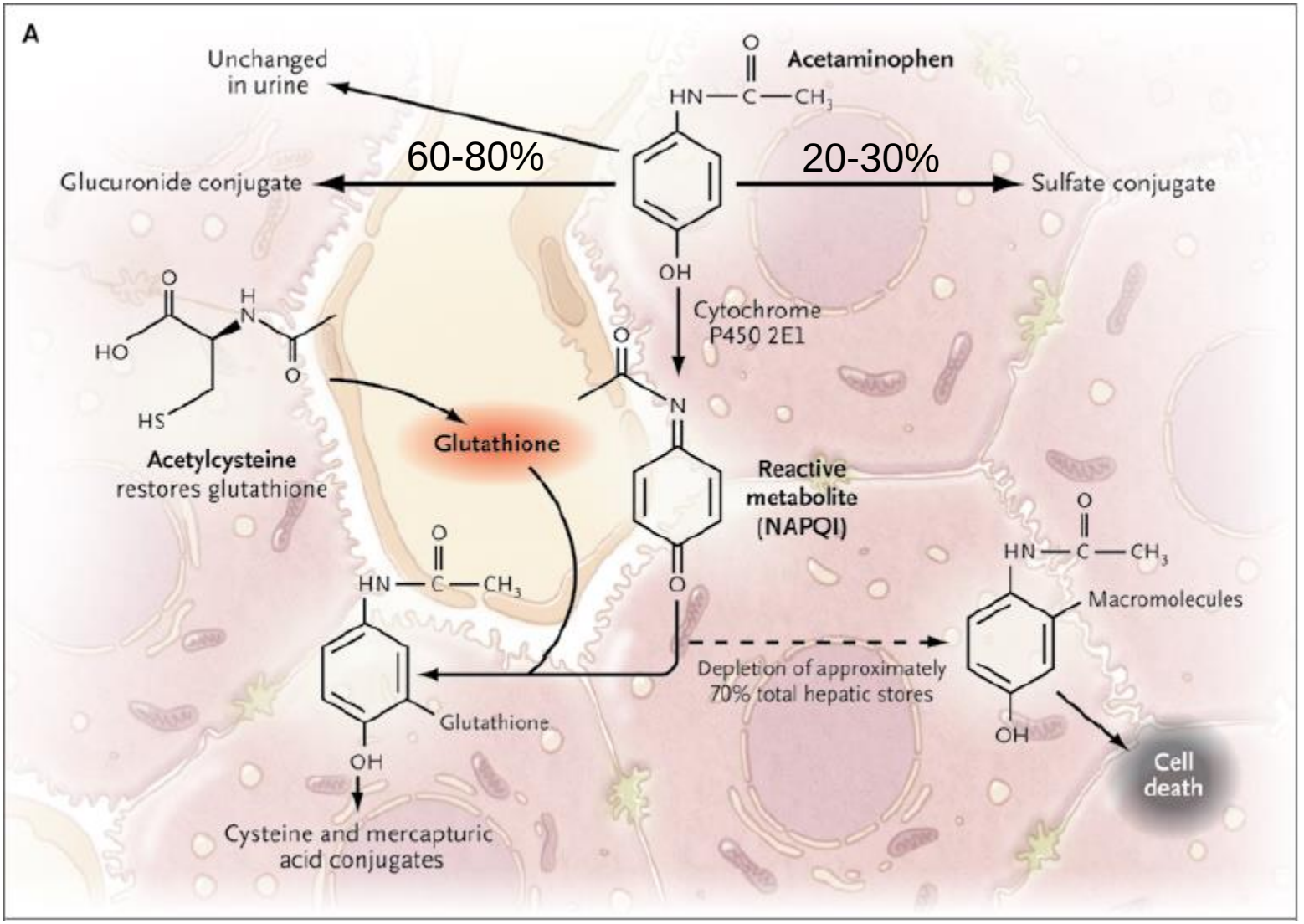
Demi-vie d'absorption: 30 minutes
Demi-vie plasmatique: 2 heures
Volume de distribution: 1l/kg
Dose recommandée (VIDAL®): 4g/j
Surdosage 6-10g/j



Objectif thérapeutique:
10-30 mg/l

Rumack et al. Hepatology 2004

Toxicité hépatique du paracétamol



Heard N Engl J Med 2008

Facteurs influençant la toxicité hépatique

Box 1 Factors that increase the risk of liver injury after an overdose of paracetamol

High chance of glutathione depletion:

- Malnourished (for example, not eating because of dental pain or fasting for more than a day)
- Eating disorders (anorexia or bulimia)
- Failure to thrive or cystic fibrosis in children
- AIDS
- Cachexia
- Alcoholism

Clinical clues: history, low body mass index, urinalysis positive for ketones, low serum urea concentration

Hepatic enzyme induction:

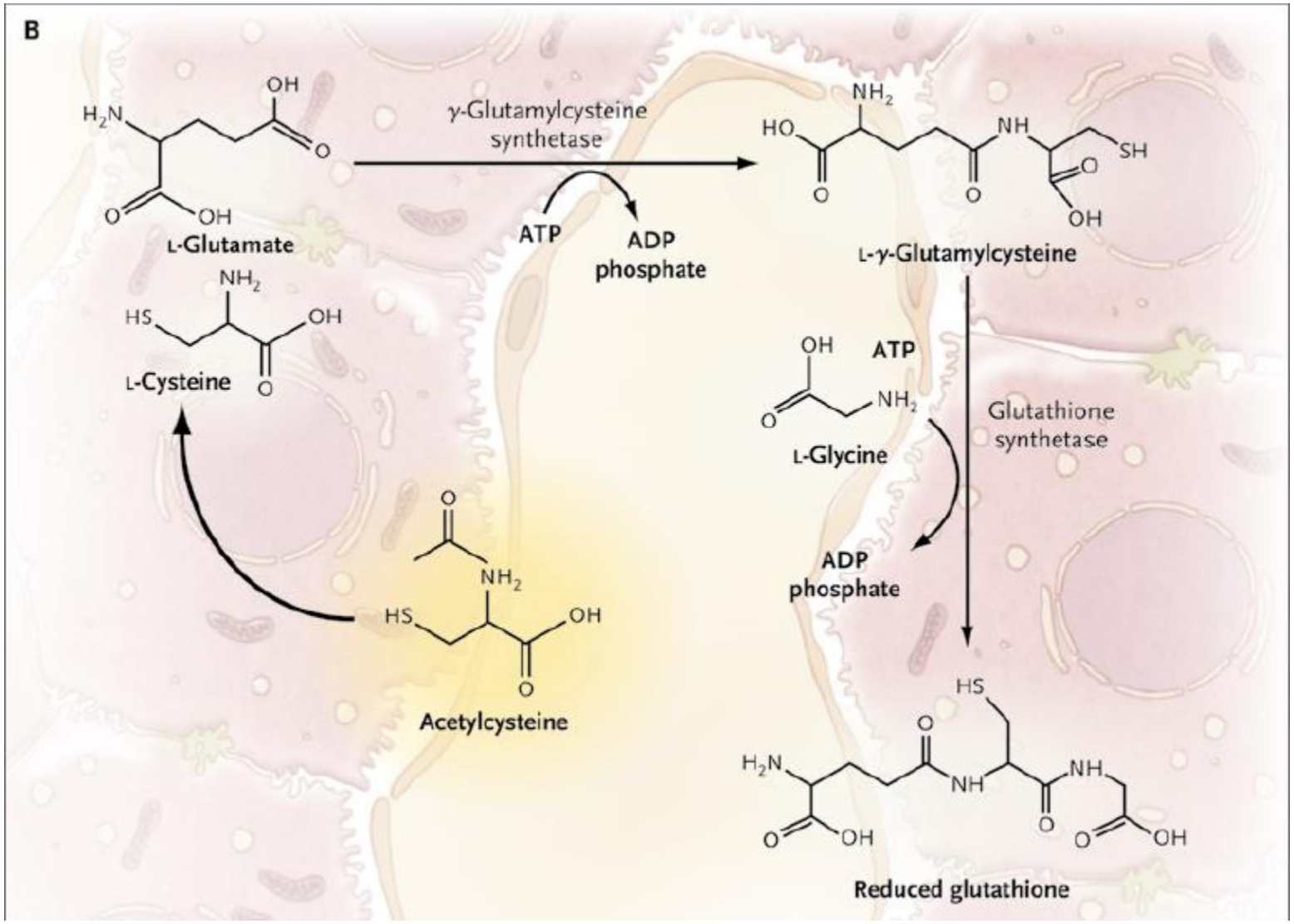
- Long term treatment with enzyme inducing drugs, such as carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, rifabutin, efavirenz, nevirapine, and St John's wort
- Regular consumption of ethanol in excess of recommended amounts

Clinical clues: history, abnormal liver function tests, increased international normalised ratio, increased γ-glutamyl transpeptidase

Abnormal renal or hepatic function at presentation

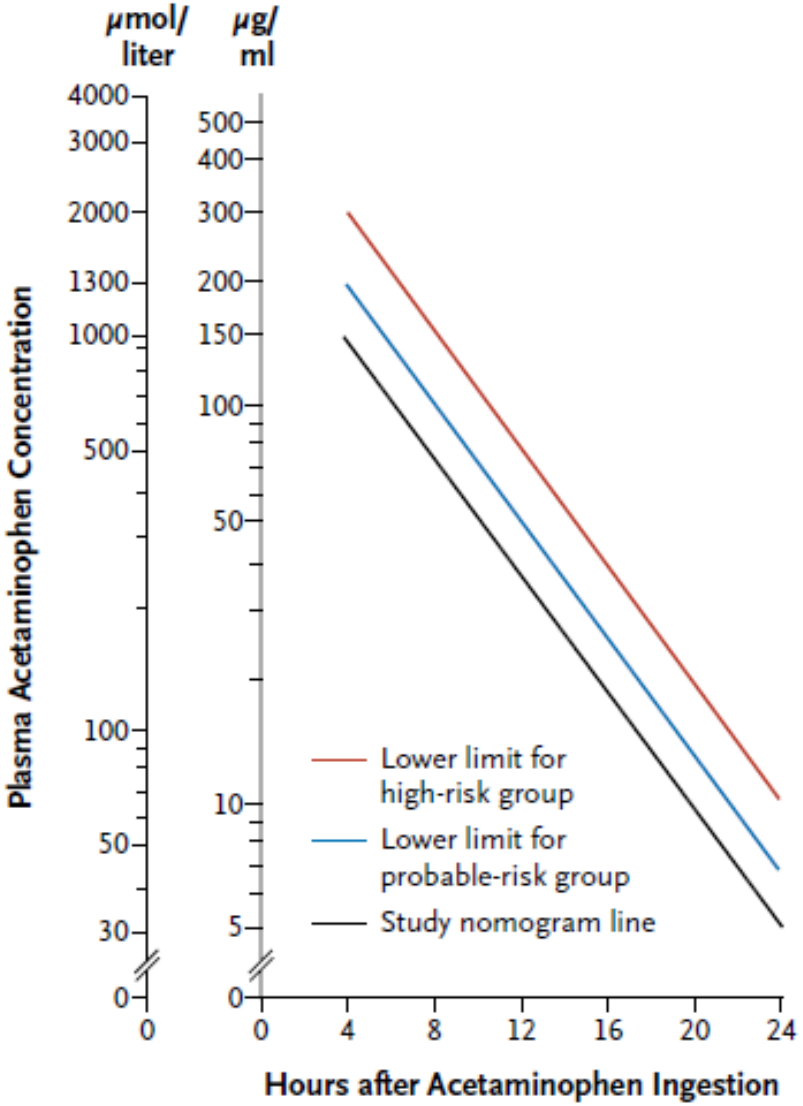
Ferner et al. BMJ 2011

N-acétylcystéine et paracétamol



Heard N Engl J Med 2008

N-acétylcystéine et paracétamol



Efficacité de la NAC:

- Etudes anciennes (Smilkstein N Engl J Med)
- Méta-analyses: Effet bénéfique mais niveau de preuve faible
- Voie orale ou IV

Problèmes des nomogrammes:

- Inadaptés en cas de prise chronique
- Inadaptés en cas de mésaventure
- Nécessitent de connaître l'heure de prise

Heard N Engl J Med 2008

Quelle dose de paracétamol?

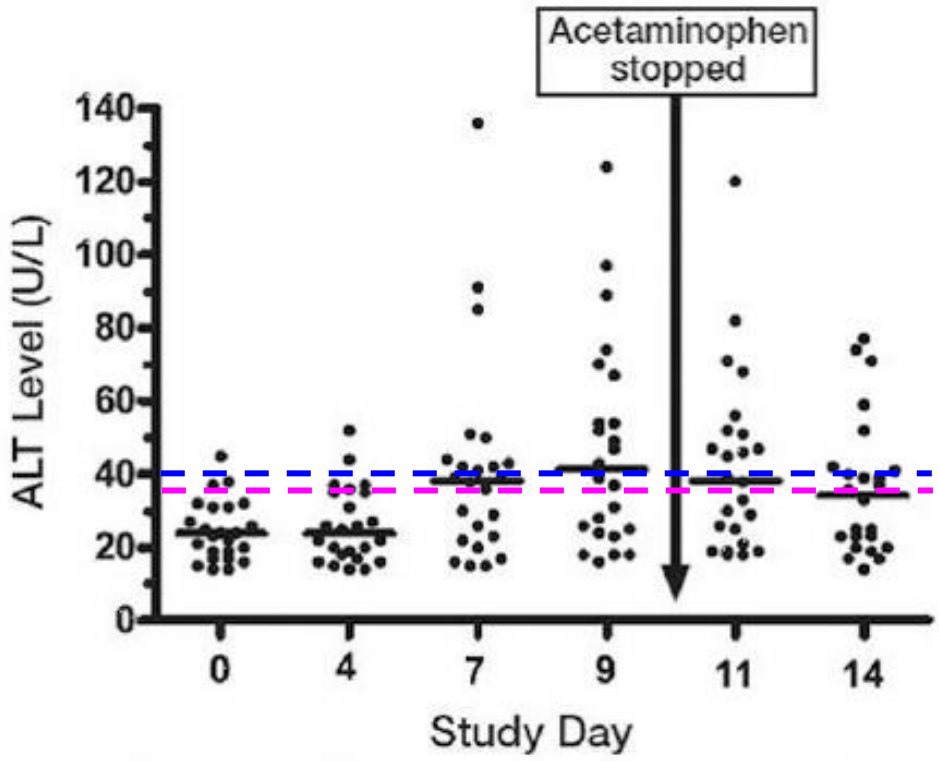
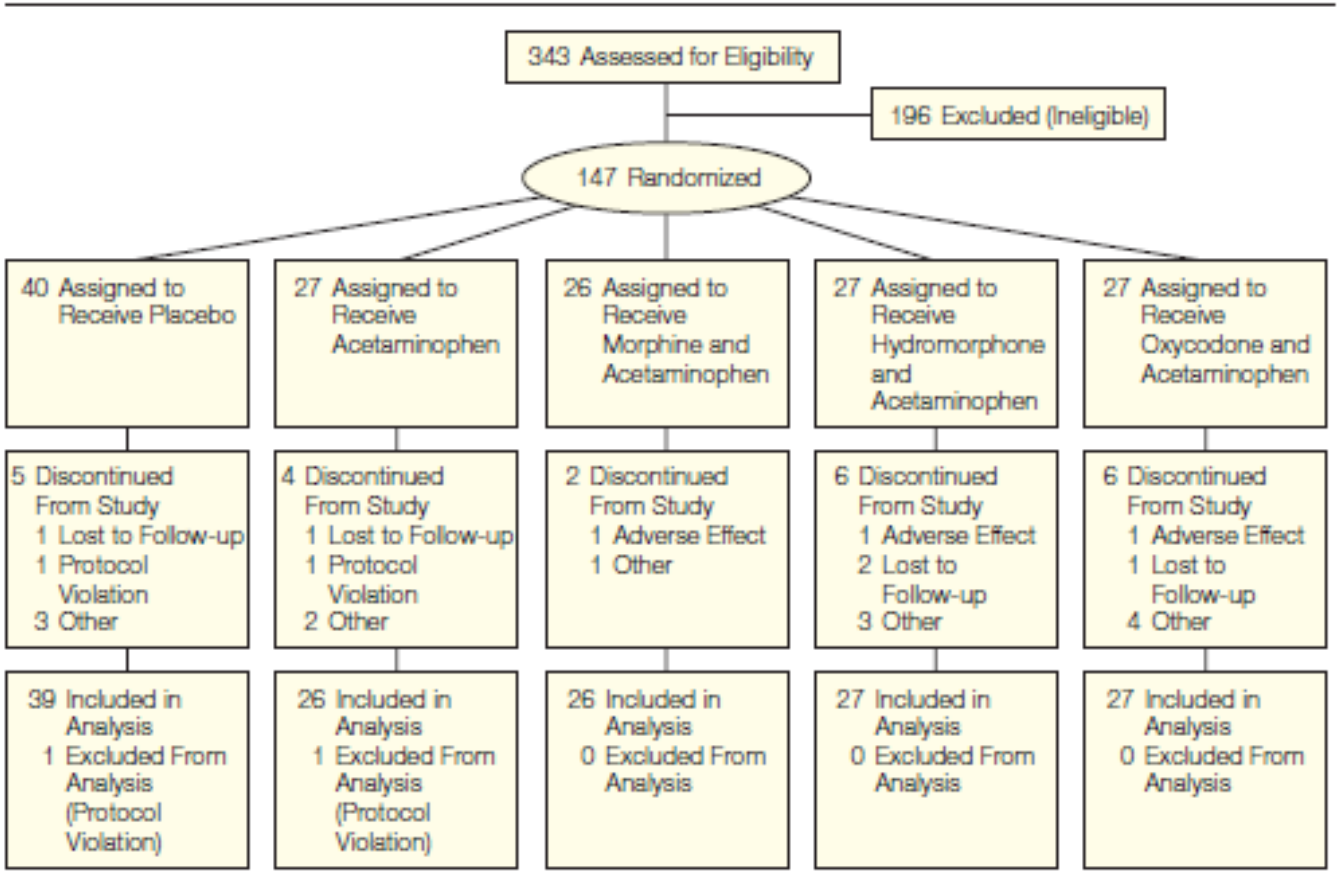


Figure 1.
Serum alanine aminotransferase (ALT) levels measured over 14 days in 24 nondrinkers administered acetaminophen 4 g/day for 10 days. Horizontal lines indicate median values; median ALT level on days 7, 9, 11, and 14 were higher than on day 0 (baseline).

Heard et al. Pharmacotherapy 2011

Quelle dose de paracétamol?



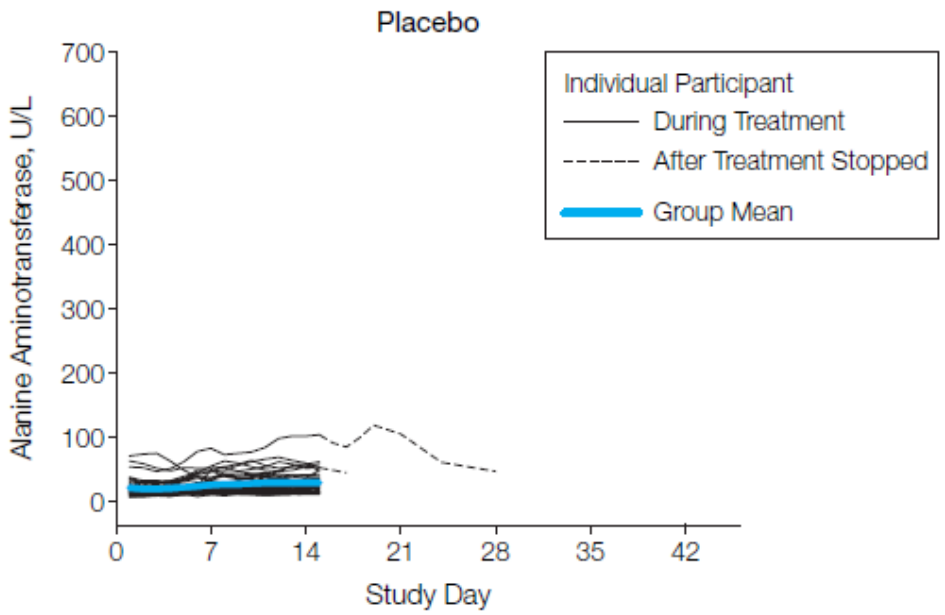
Doses:

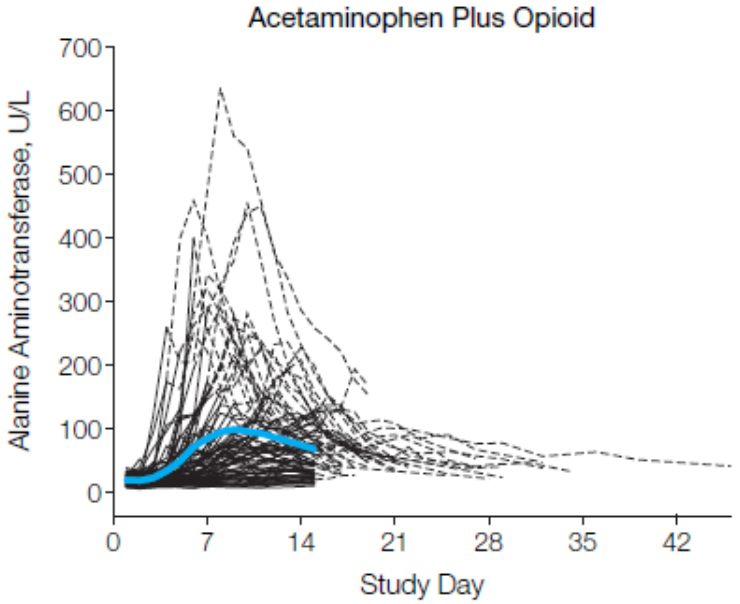
- Paracétamol: 4g/j
- Morphine: 120 mg/j
- Hydromorphone: 16 mg/j
- Oxycodone: 60 mg/j

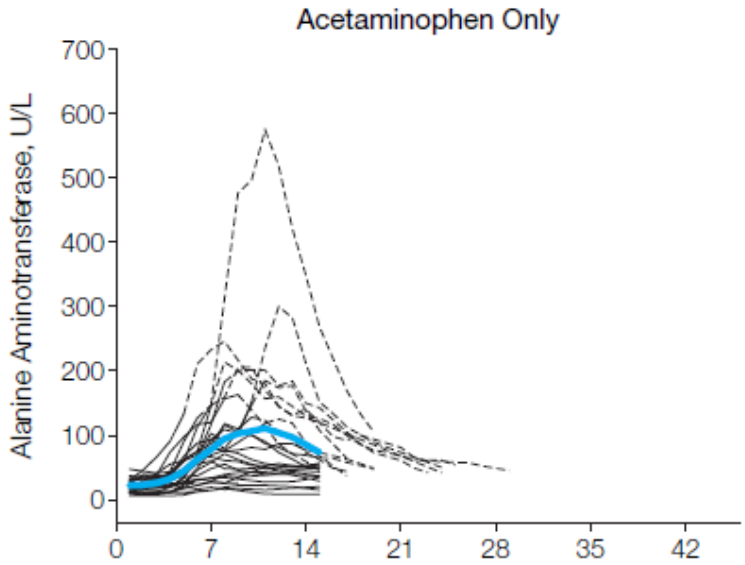
Durée 14 jours

Watkins et al. JAMA 2006

Quelle dose de paracétamol?







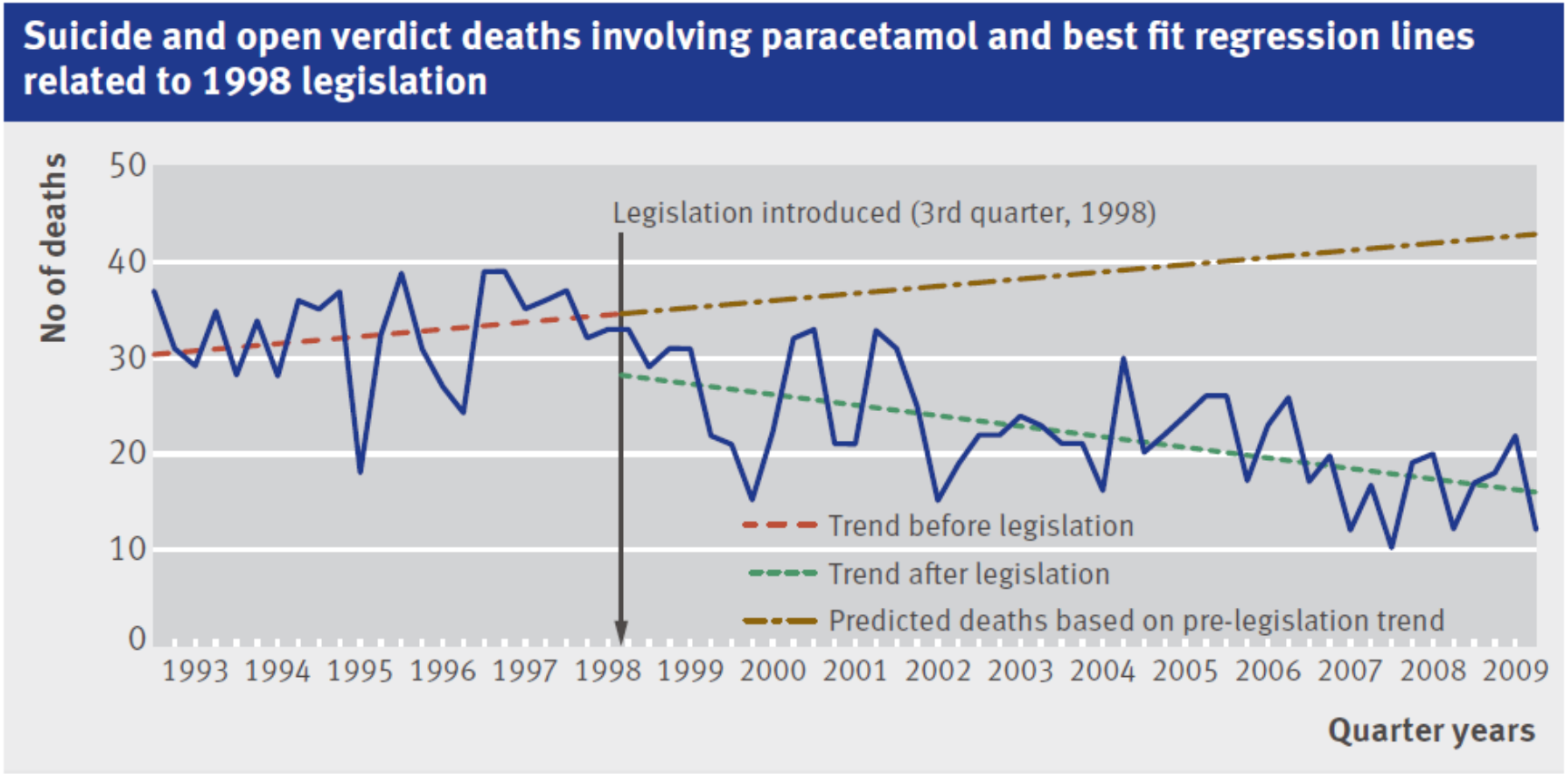
Le traitement était arrêté si ALAT >3N

"At present, I am not certain as to what is a perfectly safe dose of acetaminophen, especially when taken for more than a day or two."

Neil Kaplowitz Hepatology 2004

Watkins et al. JAMA 2006

Conditionnement du paracétamol



Loi de 1998 : 32 cp à 500mg/boîte (pharmacies) ou 16 cp/boîte (parapharmacies)

En France: pas de restriction sur la quantité délivrée mais boîtes limitées à 8g

Hawton et al. BMJ 2013

Hépatite aiguë

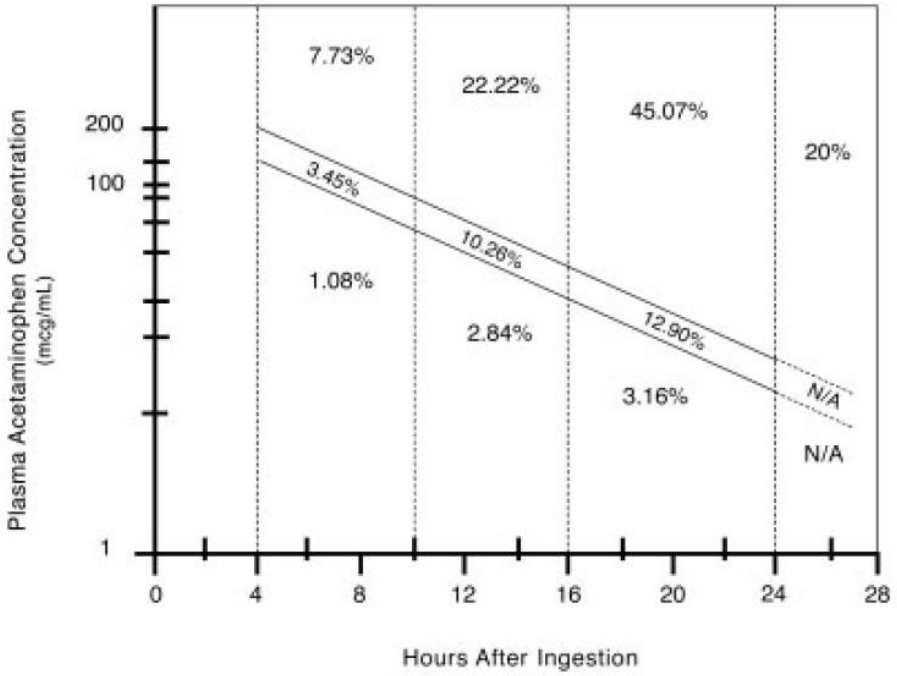


Fig. 2 Outcome Nomogram with the original nomogram line and the 25% safety line added during the nationwide NAC study. Patients were plotted at the point of their initial APAP level. Percent is the number of cases with AST greater than 1,000 IU/L at any time during their course.

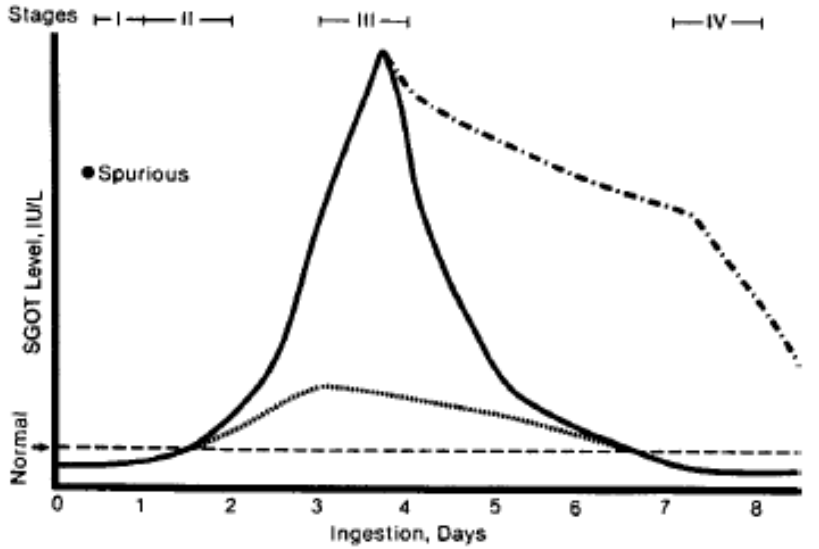


Fig. 3 Pattern of Enzyme Elevation following a single APAP overdose at time zero. Solid line represents AST in untreated cases. Dotted line represents AST in cases treated with NAC. Dashed line represents AST in non-overdose normal patients. Dot and dash line represents AST in cases progressing to fulminant hepatic failure. Single dot indicates a spurious AST as it cannot rise that rapidly after overdose.

Rumack et al. Hepatology 2004

Hépatite fulminante: clinique

Clinical and demographic features of acute liver failure according to etiologic groups. Acetaminophen-related ALF is considered hyperacute and demonstrates the very high aminotransferase and low bilirubin levels, compared to drug-induced liver injury which is more indolent.

Comparison of Different ALF Aetiology Groups

	APAP $n = 787$	Drug $n = 202$	Indeterminate $n = 219$	HepA/HepB $n = 37/123$	All others $n = 328$
Age (median)	37	47	38	48/43	45
Sex (% F)	76	66	60	46/45	73
Jaundice (Days) (median)	0	8	8	3/5	4
Coma ≥3 (%)	53	37	50	51/55	43
ALT (median)	3846	685	849	2124/1702	677
Bili (median)	4.4	19.8	22.0	12.5/19.1	14.6
Tx (%)	9	40	45	32/41	30
Spontaneous Survival (%)	67	31	27	54/24	38
Overall Survival (%)	75	68	69	84/61	65

L'hépatite fulminante au paracétamol est:
- Très cytolytique
- De meilleur pronostic
- Sans ictère

Lee Best Pract Clin Res Gastroenterol 2012

Indications de TH

Critères français

- Confusion ou coma
- Facteur V < 30% (âge > 30 ans) ou FV< 20% (si > 30 ans)

Bernuau et al 1986

Critères du King's College

- Paracétamol
  - pH < 7,3 ou Lactate > 3,5 (après remplissage)
  - OU les 3 critères suivants
    - INR >7
    - Créatinine > 300 µmol/l
    - EH grade 3-4
- Hors paracétamol:
  - INR > 6,7
  - OU 3 critères parmi:
    - Age <10 ans, âge >40 ans
    - Bilirubine > 300 µmol/l
    - INR > 3,5
    - Etio de mauvais pronostic (médicaments, hépatite virale non A non B)
    - Délai ictère-EH > 7 jours

O'Grady et al 1989

Alcool et paracétamol
Mésaventure au paracétamol

Alcool et paracétamol

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF 71 PATIENTS WHO INGESTED OVERDOSES OF ACETAMINOPHEN, EITHER ACCIDENTALLY OR IN A SUICIDE ATTEMPT.

CHARACTERISTIC	ACCIDENTAL OVERDOSE (N=21)	SUICIDAL OVERDOSE (N=50)	P VALUE
Age — yr			
Mean ±SD	34±10	29±13	
Median	36	26	0.12
Range	16–54	14–83	
Sex — F/M	11/10	37/13	0.10
Race or ethnic group			0.009*
Asian	0	4	
Black	11	9	
Hispanic	4	9	
Native American	1	0	
White	5	28	
Acetaminophen dose — g			
Mean ±SD	11±7	24±22	
Median	12	20	0.009
Range	2–30	3–125	
Acetaminophen dose ≤4 g — no. (%)	3 (14)	2 (4)	0.15
Ethanol ingestion — no./no. studied (%)			
Acute†	8/18 (44)	14/36 (39)	0.77
Chronic‡	12/19 (63)	11/44 (25)	0.009
Concurrent intoxication — no. (%)§	6 (29)	17 (34)	0.78
Intravenous drug abuse — no. (%)	4 (19)	13 (26)	0.76

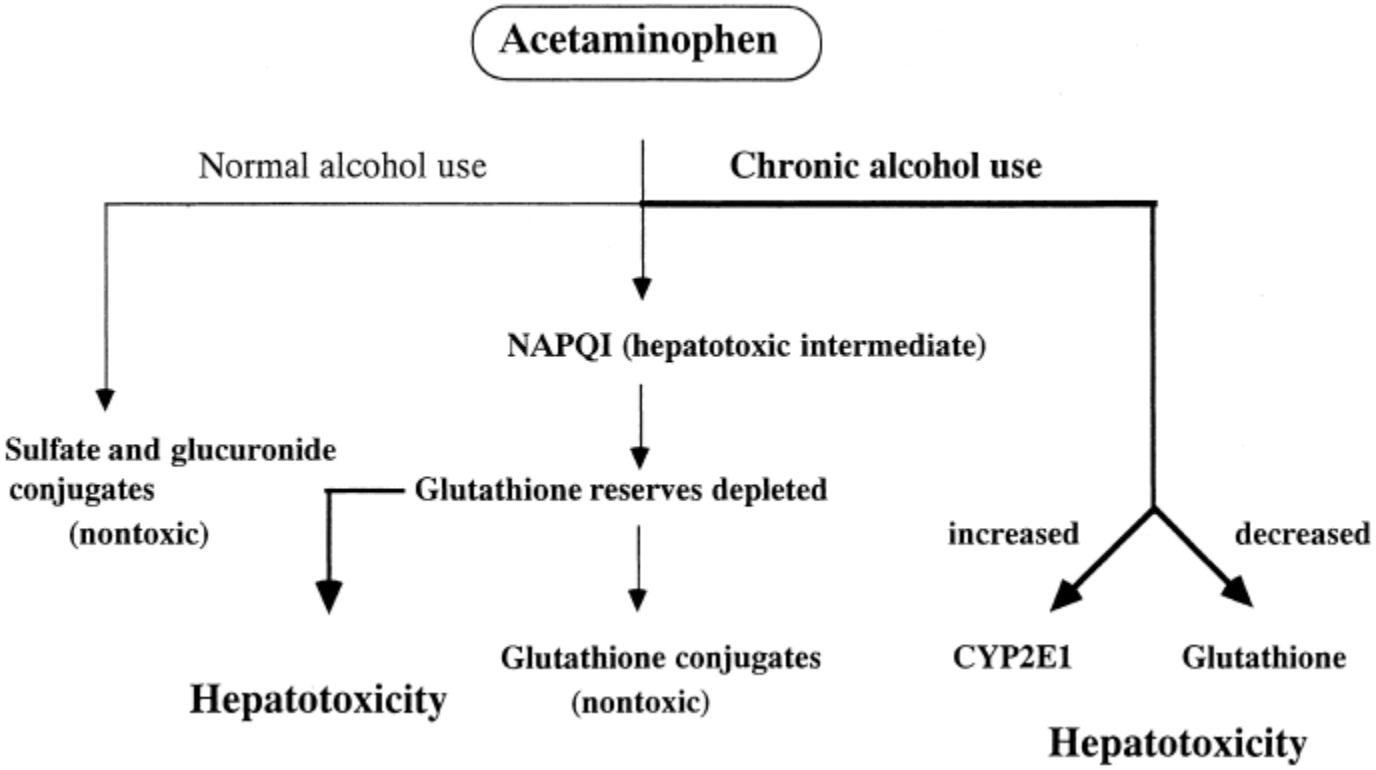
TABLE 2. CLINICAL VARIABLES PERTAINING TO THE ACCIDENTAL AND SUICIDAL OVERDOSES OF ACETAMINOPHEN IN THE STUDY PATIENTS.*

VARIABLE	ACCIDENTAL OVERDOSE (N=21)	SUICIDAL OVERDOSE (N=50)	P VALUE
History available — no. (%)	17 (81)	43 (86)	0.72
Presentation >24 hr after overdose — no./no. studied (%)†	9/14 (64)	5/35 (14)	0.001
Peak acetaminophen — mg/liter			
Mean ±SD	39±53	145±101	
Median	7	126	<0.001
Range	1–155	8–460	
Peak acetaminophen >10 mg/liter — no./no. studied (%)‡	7/15 (47)	46/49 (94)	<0.001
Peak ALT — IU/liter			
Mean ±SD	2557±3061	1384±2918	
Median	1964	26	0.003
Range	9–12,700	6–10,550	
Peak AST — IU/liter			
Mean ±SD	7430±10,309	1501±3555	
Median	3490	31	0.001
Range	19–34,720	11–15,890	
Peak ALT or AST — no. (%)			
>1000 IU/liter	13 (62)	10 (20)	0.002
>3500 IU/liter	11 (52)	7 (14)	0.002
Peak prothrombin time — sec			
Mean ±SD	25.7±18.5	18.0±12.4	
Median	18.0	13.8	0.04
Range	11.7–76.1	11.4–71.5	
Peak serum bilirubin — mg/dl			
Mean ±SD	12.0±15.1	1.4±2.4	
Median	4.2	0.7	0.004
Range	0.2–51.6	0.2–12.9	
Peak serum creatinine — mg/dl			
Mean ±SD	2.6±2.6	1.0±0.3	
Median	1.3	0.9	0.05
Range	0.6–9.4	0.5–1.7	
No. of criteria met§			0.27¶
1	9	12	
2	10	30	
3	2	8	
Acetylcysteine therapy — no. (%)	16 (76)	40 (80)	0.76
Hepatic coma — no. (%)	7 (33)	3 (6)	0.006
Death — no. (%)	4 (19)	1 (2)	0.04

La consommation chronique d'alcool semble majorer la toxicité du paracétamol

Schiødt et al. N Engl J Med 1997

Alcool et paracétamol



Autres paramètres associés:

- Temps de consultation plus tardif
- Moindre efficacité de la NAC?
- Présence d'une hépatopathie sous-jacente (incidence de la cirrhose?)

Tanaka et al. J Clin Pharm Ther 2000

Alcool et surdosage en paracétamol

Table 1. Results of Multivariate Analyses Using Age, Sex, Time to NAC, Dose, Alcohol, and Other Medication as Independent Variables in 645 Cases of Single-Dose Acetaminophen Poisoning Showing Risk Factors and Protective Factors for Variables Associated With Clinical Outcome

Variable	Risk Factors	Protective Factors
Prothrombin index	T-NAC (−0.43) > dose (−0.22), CAA (−0.09)	AAU (0.16)
Alanine transaminase	T-NAC (0.36) > dose (0.22)	AAU (−0.11)
Bilirubin	T-NAC (0.33), CAA (0.19) > age (0.12)	AAU (−0.08)
Creatinine	T-NAC (0.27), CAA (0.21)	AAU (−0.11)
HE	T-NAC, CAA, age, dose	AAU
Death or liver transplant	Age, CAA, T-NAC	AAU

NOTE. Standardized regression coefficients from the multiple regression analyses are given in parentheses. >, the first variable contributes significantly more to the risk than the second variable.

Abbreviations: T-NAC, time to NAC; CAA, chronic alcohol abuse; AAU, acute alcohol use.

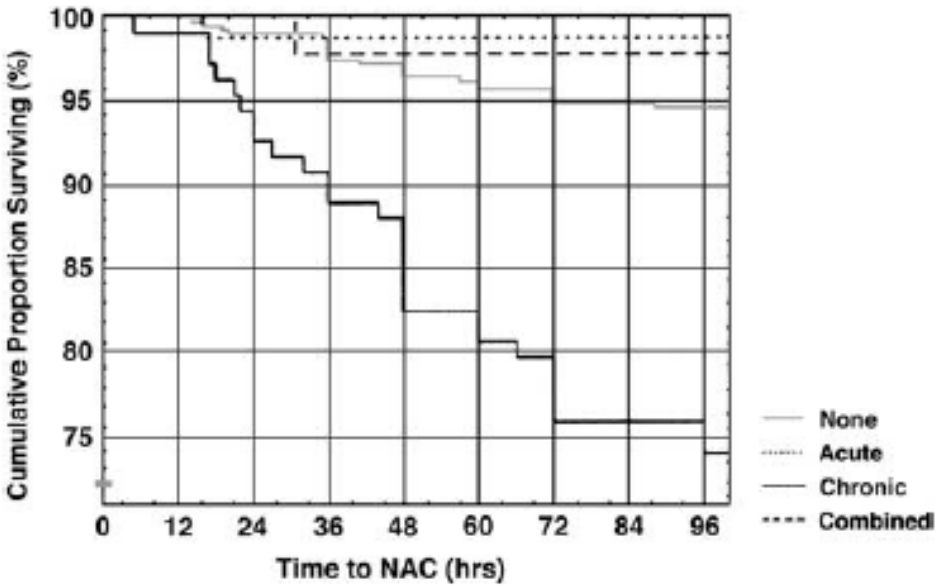


Fig. 2. The cumulative survival rates for every time to NAC for each alcohol subgroup. There was a significant difference between the chronic and other subgroups ($P < .0001$ by Cox's F test).

La consommation chronique d'alcool est associée à une évolution péjorative et à une moins bonne survie

Schmidt et al. Hepatology 2002

Alcool et surdosage en paracétamol

Table 3. Results of Multivariate Analyses Using Age, Sex, Time to NAC, Dose, Alcohol, and Other Medication as Independent Variables in 157 Patients With and 488 Patients Without Regular Abuse of Alcohol Showing Risk Factors and Protective Factors for Variables Associated With Clinical Outcome

	With Regular Alcohol Abuse		Without Regular Alcohol Abuse
Variable	**Risk Factors**	**Protective Factors**	**Risk Factors**
Prothrombin time	T-NAC (−0.31), dose (−0.17)	Acute alcohol use (0.46)	T-NAC (−0.45) > dose (−0.22)
Alanine transaminase	Dose (0.19)	Acute alcohol use (−0.49)	T-NAC (0.44) > dose (0.20)
Bilirubin	T-NAC (0.33)	Acute alcohol use (−0.26)	T-NAC (0.33) > dose (0.12), age (0.11)
Creatinine	T-NAC (0.23)	Acute alcohol use (−0.31)	T-NAC (0.28) > dose (0.10)
HE	T-NAC, age	Acute alcohol use	T-NAC, dose, age
Death or OLT	Age, T-NAC	Acute alcohol use	T-NAC

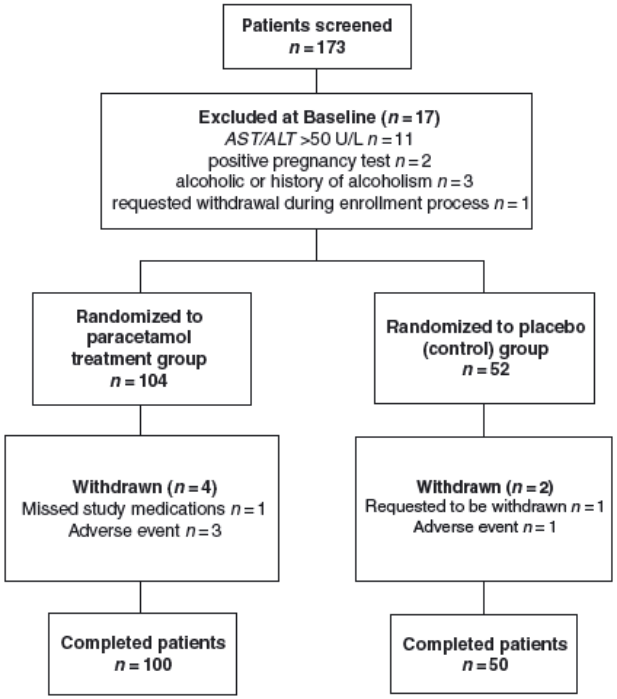
NOTE. Standardized regression coefficients from the multiple regression analysis are given in parentheses. >, the first variable contributes significantly more to the risk than the second variable.

Abbreviations: T-NAC, time to NAC; OLT, liver transplant.

Chez le patient consommateur excessif, la consommation aiguë d'alcool est associée à une meilleure évolution

Schmidt et al. Hepatology 2002

Alcool et paracétamol



Patients avec consommation d'alcool de 10 à 30 g/j
Randomisation: placebo ou paracétamol 4g/j
Durée de traitement: 10j

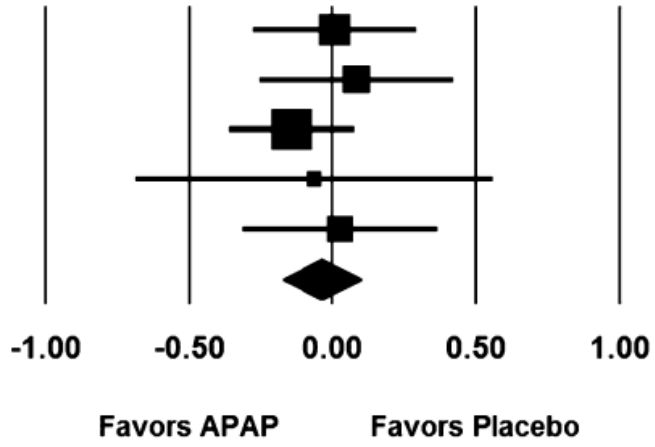
Table 2. Baseline, day 4 and day 11 liver function tests for control and paracetamol groups

	Control Mean (s.d.)			Paracetamol Mean (s.d.)		
Variable	Baseline	Day 4	Day 11	Baseline	Day 4	Day 11
ALT (IU/L)	22.4 (8.2)	21.7 (8.2)	21.6 (7.9)	21.3 (7.6)	21.0 (7.5)	30.0 (19.6)
AST (IU/L)	22.0 (5.8)	22.7 (8.9)	21.8 (5.3)	21.5 (5.6)	22.6 (5.8)	28.5 (24.7)
Total bilirubin* (μmol/L)	9.75 (5.13)	10.09 (5.81)	10.60 (7.52)	10.26 (6.50)	9.92 (5.64)	10.60 (7.52)
Alkaline phosphatase (IU/L)	69.0 (16.9)	68.6 (16.1)	68.1 (15.5)	68.1 (17.9)	65.8 (17.6)	66.2 (17.5)
Total protein† (g/L)	73 (9.5)	72 (3.5)	72 (3.6)	73. (9.6)	72 (4.2)	72 (3.9)

Heard et al. Aliment Pharmacol Ther 2007

Alcool et paracétamol

Study name	Std diff in means	Variance	Lower limit	Upper limit	APAP	Pla	Total
Kuffner 2001[10]	0.012	0.021	-0.271	0.294	98	95	193
Heard 2007[9]	0.087	0.029	-0.249	0.423	102	51	153
Kuffner 2007[11]	-0.141	0.012	-0.357	0.075	262	120	382
Bartels 2008[7]	-0.061	0.100	-0.682	0.560	21	19	40
Dart 2010[8]	0.029	0.030	-0.311	0.369	68	65	133
Overall	-0.037	0.005	-0.173	0.099	551	350	901



Méta-analyse des essais randomisés chez les patients avec consommateurs excessifs
Hétérogénéité concernant la définition de la consommation chronique

Rumack et al. Pharmacotherapy 2012

Mésaventure au paracétamol

- Première description:

Zimmermann et Maddrey Hepatology 1995: étude rétrospective de cas rapportés

- Existence remise en question par plusieurs auteurs car:
  - Difficultés d'interrogatoire
  - Consultation parfois tardive
  - Niveau de preuve faible

Conclusion

- Les hépatites médicamenteuses sont fréquentes et probablement sous-déclarées
- La « loi de Hy » aide à identifier les toxicités médicamenteuses des nouvelles molécules
- Les critères d'arrêt sont bien codifiés (FDA)
- L'hépatite au paracétamol est fréquente et s'observe en cas de surdosage aigu
- La mésaventure au paracétamol est méconnue et principalement observée chez le buveur excessif
- Les prescriptions de paracétamol doivent être prudentes dans cette population