99年北縣藥師公會持教課程

止痛藥物引起肝毒性之案例討論

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2010.05.30

Outline

- Presentation of Case
- ADR
- DILD
- Case comparison
- Conclusion

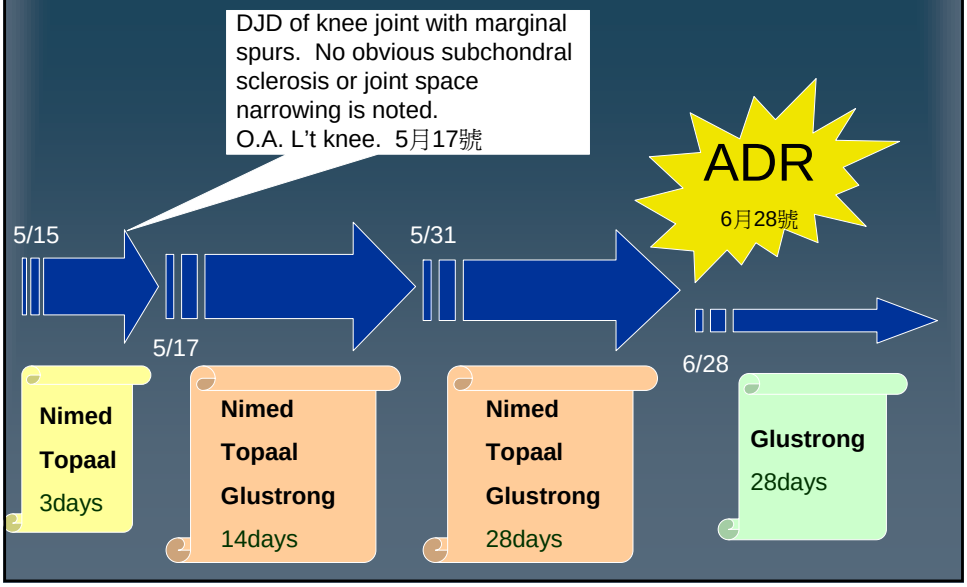
Case Report

- Patient Name： 劉先生
- Age：54yrs
- Weight: 55kg
- Outpatient care: since 91/12/21
- Alcohol/Smoking/Allergy: NKA

Case Report

- Chief complaint: Arthropathy
- Impression:
  Pain of L't knee for 10 days(96.05.15)
- Medication: 96.05.15~96.06.28
  Nimed(Nimesulide) 100mg 1# BID
  Topaal(Alginic acid) 200mg 1# BID
  Glustrong Cap(Glucosamine sulfate) 250mg 1# BID*

Case Report: Medication



Past History

- Family history of hyperlipidemia
  (Mother: CVA ; Father: stroke ;
  Elder sister: hyperlipidemia)
- Hyperchloesterolaemia:
  Lipitor 0.5# QD (92.01.04~)
- Essential hypertension:
  Plendil 1# QD (91.12.21~92.11.07)
  Diovan 1# QD (92.11.07~95.08.28)
  Aprovel 1# QD (95.08.28~)

Examination

Date	Deta
96.07.20	**ALT/AST:134/35**
96.07.06	HBV(-),HCV(-),**ALT/AST:570/153**,TC:216,TG:71
96.06.28	**ALT:846**,TC:177,TG:33,HDL:51,LDL:124
95.11.26	ALT:23,TC:170,TG:30,HDL:54,LDL:118,AC:88
95.04.09	TC:195,TG:32,HDL:61,LDL:129
94.08.15	TC:176,TG:88,HDL:47,LDL:117
92.09.27	Sono:WNL
92.09.20	UGI scope: gastritis
91.12	chol:243,TG:80,HDL:49,LDL:167,UA:6.0
91.11	chol:280,LDL:203

ADR

- Occur: about 1 month(96.5.15~96.6.28)
- Dosage: 200mg/day for 42days
- Remission:
  after DC Nimed, about 1 month(96.6.28~96.8)
  {ALT/AST:134/35}
- Nimesulide-induced acute hepatitis?

DILD

(Drug-Induced Liver Disease)

Epidemiology

- Approximately 10% of cases of mild to moderate alterations of hepatic biochemical/laboratory profiles(including hepatitis) are attributed to medicinal agents.{pt>50yrs, 40% of cases}
- Approximately 50% of cases of acute fulminant hepatic failure are due to medicinal agents.(USA)
- In the geriatric population, medical agents are responsible for 20% of cases of jaundice and 25% of cases of fulminant hepatic failure.(USA)
- Worldwide, the overall frequency of DILD as a percentage of all drug reaction is 3~9%. Adverse drug reactions are responsible for 2~16% of all hospital admissions.

Risk Factors for DILD

- Age > 60 for INH, nitrofurantoin
- Peds for valproate, salicylates, ceftriaxone
- Pregnancy for tetracyclines
- Rifampin + INH, macrolides + estrogens
- FHF
  - risk factors (female, hepatocell.damage, high baseline bili conc.)
  - antibacterials, ecstacy and anti-TB

Clinical Monitoring-LFTs

- The liver contains thousands of enzymes, some of which are present in the serum.
- The elevation of a given enzyme activity in serum is thought to primarily reflect its increased rate of entrance into serum from damaged liver cells.
- Serum enzymes can be grouped into two categories: those reflective of damage/necrosis or those reflective of cholestasis.

Enzymes that detect hepatocellular necrosis

- **AST/(SGOT)-**aspartate aminotransferase {mitochondria}; found in heart and liver.
  (In contrast to viral hepatitis, serum AST exceeds ALT in extensive necrotic injury such as occurs in alcoholic hepatitis)
- **ALT/(SGPT)-**alanine aminotrasferase {microsomal portion}; mostly in liver. →more specific for liver disease than AST
  (In acute viral hepatitis without extensive necrosis, ALT exceeds AST, whereas AST exceeds ALT in alcoholic hepatitis owing to release of mitochondrial AST)
- **LDH**-lactate dehydrogenase; found in same tissues as SGOT; generally poor LFT; also increased in heme malignancies, anemias, MI, rhabdomyolysis, pulmonary infarct, shock

Enzymes that detect Cholestasis

- **Alk Phos (AP)-**alkaline phosphatase
  - Liver and bone mainly, also kidney, placenta, leukocytes
  - Bone-> Paget's, hyperparathyroidism, rickets, osteomalacia
  - AP level is a sensitive indicator of cholestasis
- **GGT**-gamma-glutamyl transpeptidase
  - Found in liver, seminal vesicles, pancreas, spleen, heart, brain
  - Confirms liver source of incr. alk phos. (e.g. bone disease, childhood, pregnancy where alk. phos. is normally increased)
  - γ-GT is often increased in alcoholics

Spectrum of Enzyme Activity

- Cytotoxic-overt damage to hepatocytes
- Necrosis-zonal, diffuse or massive
- Steatosis-fat infiltration

- Cholestatic-arrested bile flow

- Mixed-features of both

Non-specificity of LFTs

Enzyme	Cholestasis	Necrosis
Alk Phos	XX	X
GGT	XX	X
AST	X	XX
ALT	X	XX
LDH	X	XX

Patterns of LFT Abnormalities

1. Hepatitis/hepatocellular:
   (ALT/ULN) ÷ (AP/ULN) ≥ 5

2. Cholestasis:
   equation result ≤ 2

3. Mixed:
   equation result > 2 to < 5

(ULN = upper limit of normal)

Bilirubin (pigment, byproduct of heme-protein breakdown)

- Generally, total serum bilirubin is not a sensitive indicator of hepatic dysfunction
- Cholestasis
- Check skin, sclera

Prothrombin Time (INR)

- Increase in PT/INR secondary to dietary deficiency of K, destruction of intestinal bacteria→ K, decreased K absorption due to decreased bile salts, malabsorption or decreased utilization of K secondary to liver cell destruction.
- Usually takes severe disease before PT/INR increased
- Lack of response of PT/INR to IV vit. K is of grave prognostic significance.

Types of DILD

- Predictable (intrinsic)
  -relatively high occurrence rate, often related to dose
  - Direct
  - Indirect--bioactivation
- Unpredictable (idiosyncratic)
  -generally no association with dose

Types of Hepatic Injury

- Centrolobular necrosis
  (commonest and worst outcome as death/transplant in 12% if jaundiced at diagnosis)

- Drugs:
- Predictable-Acetaminophen
- Unpredictable-Methyldopa, INH, Halothane, PTU

Cholestasis

- Drugs:
- Predictable-Chlorpromazine, retinoids
- Unpredictable-Sulfonamides, Macrolides, Amoxicillin-clavulanate, Penicillinase-Resistant Penicillins, TMP/SMX, Methimazole

Steatonecrosis

- Drugs:
- Predictable-Ethanol, Valproic Acid, Amiodarone, Tetracyclines, Methotrexate

Toxic Hepatitis

- Drugs:
- Unpredictable-Ketoconazole, Nitrofurantoin, INH, Methyldopa, TMP/SMX

Hepatic Vascular Disorders

- **Drugs**:
  - Predictable-Oral androgens/anabolic steroids
  - Unpredictable-Azathioprine, combination cancer chemotherapy
- **Types**:

  Hepatic vein thrombosis (Budd-Chiari syndrome), Peliosis hepatis, veno-occlusive disease

Gallstones

- Fibrates-true (cholesterol)
- Ceftriaxone (pseudo)

Hepatotoxic Herbals

- Adulterated Chinese medicine
- (N-nitrosofenfluramine)

--See appended table from Feb. 2002 issue of Seminars in Liver Disease

CASE COMPARISON

ADR

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- Dosage: 200mg/day for 42days
- Remission:
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Examination

Date	Deta
7.20	**ALT/AST:134/35**
7.06	HBV(-),HCV(-), **ALT/AST:570/153**,TC:216,TG:71
6.28	**ALT:846**,TC:177,TG:33,HDL:51,LDL:124

96.07.06: Normal (SONO)

liver, intrahepatic bile duct, common bile duct, gallbladder, portal vein, pancreas, spleen, kidney → all negative(-)

Nimesulide-induced acute hepatitis

(Van Steenbergen et al, 1998)

- Six patients developed ACUTE HEPATITIS after taking nimesulide 200 mg/day.
- Hepatic injury first became apparent within 10 to 15 weeks after therapy initiation in 5 of the patients.
- Symptoms appeared 1 week after beginning a second course of nimesulide in a patient who had taken the drug approximately 2 months prior for a period of 1 week.
- Clinical presentation was characterized primarily by jaundice, which was accompanied by pruritus, asthenia, anorexia, nausea, vomiting, and/or increased eosinophilia.

Nimesulide-induced acute hepatitis

(Van Steenbergen et al, 1998)

- One patient also developed ascites and peripheral edema, another was found to have previously unrecognized asymptomatic biliary cirrhosis, and one died of an unresectable pancreatic adenocarcinoma that was detected during clinical assessment.
- The two patterns of liver injury identified were hepatocellular necrosis with centrilobular or panlobular lesions in all four females, and severe intrahepatic cholestasis with centrilobular canalicular and hepatocellular bilirubinostasis in the two males.
- Liver enzymes eventually returned to normal in 5 of the patients who were observed for up to 17 months. The causal relationship to nimesulide therapy was assessed as highly probable in 1 patient, probable in 4 patients, and possible in 1 patient.

TABLE 1

Clinical, laboratory and histologic data in six patients with nimesulide-induced liver disease

Histologic pattern	Case	Age	Sex	Clinical features				Laboratory features					Histologic features			
				Duration Rx (weeks)	Jaundice	Pruritus	Evidence of hypersensitivity	Eosinophilia (%) (N 0–6)	Bilirubin (mg/dl)	AlkPhos (×N)*	AST (×N)*	ALT (×N)*	Necrosis Localization Extent	Inflammatory infiltration Localization Degree	Infiltration with eosinophils	Bilirubinostasis Localization Degree
Hepatocellular necrosis																
	1	69	F	10	Yes	No	No	0.4	11	1.4	10.6	14.6	Perivenular bridging	Mononuclear Mild, portal Mild, perivenular	No	Absent
	2	39	F	3	No	No	Yes	15.8	2	2.7	4.1	9.6	Perivenular bridging	Mononuclear Mild, portal Dense, perivenular	Yes	Absent
	3	71	F	15	Yes	No	No	1.0	30	1.8	34.5	16.2	Perivenular bridging	Mononuclear Mild, portal	No	Absent
	5	81	F	15	Yes	No	No	5.0	7	1.6	28.2	22.9	Panlobular bridging	Mononuclear Variable, portal	No	Absent
Pure cholestasis																
	4	39	M	1	Yes	Yes	No	5.0	12	2.0	4.4	12.4	Absent	Absent	No	Perivenular, severe Canalicular Hepatocytes Kupffer cells
	6	75	M	5	Yes	Yes	No	9.0	6	4.4	1.8	3.2	Absent	Mononuclear Mild, portal	Yes	Perivenular, severe Canalicular Hepatocytes

Paget's

* Enzyme activities are standardized by dividing measured values by the upper limit of normal so that values are expressed as multiples of the upper limit of normal.

➢**References: Nimesulide-induced acute hepatitis: evidence from six cases**

Journal of Hepatology 1998; **29**: 135–141

Naranjo scale	是	否	不知
1.以前是否有關於此種不良反應確定的研究報告？	+1	0	0
2.此種不良反應是否於服藥之後發生？	+2	-1	0
3.當停藥或服用此藥之解藥，不良反應是否減輕？	+1	0	0
4.停藥一段時間再重新服用此藥，同樣的不良反應是否再度發生？	+2	-1	0
5.有沒有其他原因(此藥品以外)可以引起同樣的不良反應？	-1	+2	0
6.當給予安慰劑時，此項不良反應是否也會再度發生？	-1	+1	0
7.此藥品的血中濃度是否達到中毒劑量？	+1	0	0
8.對此病人而言，藥品劑量與不良反應的程度是否成正向關係？	+1	0	0
9.病人過去對同樣或類似藥品是否也產生同樣的不良反應？	+1	0	0
10.此項不良反應是否有客觀的證據？	+1	0	0

總分=4分

TABLE 2

Causality assessment in six patients with apparent nimesulide-induced liver injury, according to Danan et al. (6)

Parameters	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6	
	Parameter	Score	Parameter	Score	Parameter	Score	Parameter	Score	Parameter	Score	Parameter	Score
Hepatocellular necrosis												
Time from onset of drug administration (days) (5–90 days: +2, < 5 or >90 days: +1)	70	2	21	2	105	1			105	1		
≥50% Decrease of the difference between the peak of the most elevated AST/ALT and the upper limit of normal (days) (< 8 days: +3, < 30 days: +2)	8	3	30	2	8	3			8	3		
Use of alcohol (yes: +1, no: 0)	No	0	No	0	No	0			No	0		
Cholestasis												
Time from onset of drug administration, at first treatment (days) (5–90 days: +2, < 5 or >90 days: +1)											35	2
Time from onset of drug administration, at N-treatment (days) (<90 days: +2, >90 days: +1)							7	2				
Decrease of the difference between the peak total bilirubin and the upper limit of normal (stable or no information: 0)							Stable at 1 month	0			Stable at 1 month	0
Use of alcohol or pregnancy (yes: +1, no: 0)							No	0			No	0
Age (years) (>55: +1, <55: 0)	69	1	39	0	71	1	39	0	81	1	75	1
Associated drugs (none, no information, chronology not compatible: 0)	Chronology not compatible	0	None	0	None	0	None	0	None	0	None	0
Non-drug-related causes group I												
Hepatitis A IgM	No		No		No		No		No		No	
Hepatitis B surface antigen	No		No		No		No		No		No	
Hepatitis C antibodies	No		No		No		No		Yes		No	
Biliary obstruction on sonography	No		No		No		No		No		No	
Alcohol abuse	No		No		No		No		No		No	
Recent acute hypotension	No		No		No		No		No		No	
Total group I causes excluded	6		6		6		6		5		6	
Non-drug-related causes group II												
Complications of associated disease	No		No		No		Yes		No		No	
Evidence for CMV, Herpes Epstein Barr virus	No		No		No		No		No		No	
Total group II causes excluded	2		2		2		1		2		2	
Drug-related causes (all group I and II causes excluded: +2, all group I causes excluded: +1, 4 or 5 group I causes excluded: 0)		2		2		2		1		0		2
Previous publication on liver injury (yes: +1)		1		1		1		1		1		1
Total score		9		7		8		4		6		6
Causality assessment designation (>8: highly probable, 6–8 probable, 3–5 possible)	Highly probable		Probable		Probable		Possible		Probable		Probable	

Nimesulide-induced acute hepatitis(cont'd**)**

Table I. Summary of patient characteristics.

Characteristics	Patient 1	Patient 2	Patient 3
Age (years)	54	71	74
Gender	Male	Female	Female
Race	Chinese	Chinese	Chinese
Duration of nimesulide ingestion	19 days	Unknown	28 days (consumed over a 6-week period, with a 2-week interruption in between)
Drug consumed up to time of admission	Yes	Yes	Yes
Presenting complaint	Jaundice	Jaundice	Jaundice
Duration of jaundice prior to admission	1 days	14 days	2 days
Other symptoms (Duration preceding admission)	Nausea; dyspepsia (2 weeks)	None	Drowsiness (2 days)
Preceding concurrent drugs (all stopped prior to onset of symptoms)	Nil	TCM[a]	Diclofenac
Developed hepatic encephalopathy	No	No	Yes
Management	Dechallenge	Dechallenge	Dechallenge; MARS[b]
Peak bilirubin (umol/L) (time of occurrence from admission)	62 (Day 7)	53 (Day 9)	775 (Day 24)
Peak ALT[c] / AST[d] (xULN[e]) (time of occurrence from admission)	31 / 21 (Day 2)	27 / 26 (Day 6)	23 / 50 (Day 1)
Time from day of hospitalisation till resolution of liver function abnormalities	42 days	38 days	–
Outcome	Resolved	Resolved	Died

[a] Traditional Chinese medication
[b] Molecular adsorbent recirculating system
[c] Alanine transferase
[d] Aspartate transferase
[e] Multiples of the upper limit of normal

Nimesulide-induced hepatotoxicity and fatal hepatic failure: Singapore Med J 2007; 48(6) : 582

藥品不良反應評檢

- 不良反應種類:
  Hepatotoxicity
- 藥品不良反應型態
  B .該藥品在一般治療劑量正常服用時，產生非已知藥理作用的其他副作用
- 嚴重程度:
  輕度(無需治療，不用解藥)

Naranjo scale	是	否	不知
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7.此藥品的血中濃度是否達到中毒劑量？	+1	0	0
8.對此病人而言，藥品劑量與不良反應的程度是否成正向關係？	+1	0	0
9.病人過去對同樣或類似藥品是否也產生同樣的不良反應？	+1	0	0
10.此項不良反應是否有客觀的證據？	+1	0	0

總分=4分

Nimesulide

- Nimesulide (4-nitro-2-phenoxymethanesulphonamide) is one of the newer classes of non-steroidal anti-inflammatory drugs (NSAIDs) with preferential cyclo-oxygenase-2 (cox-2) selectivity.
- Although not entirely unlike the newer cox-2 inhibitors (such as celecoxib, rofecoxib), which have 400- to 800-fold selectivity, nimesulide selectivity for cox-2 is in the order of 5- to 16-fold only.

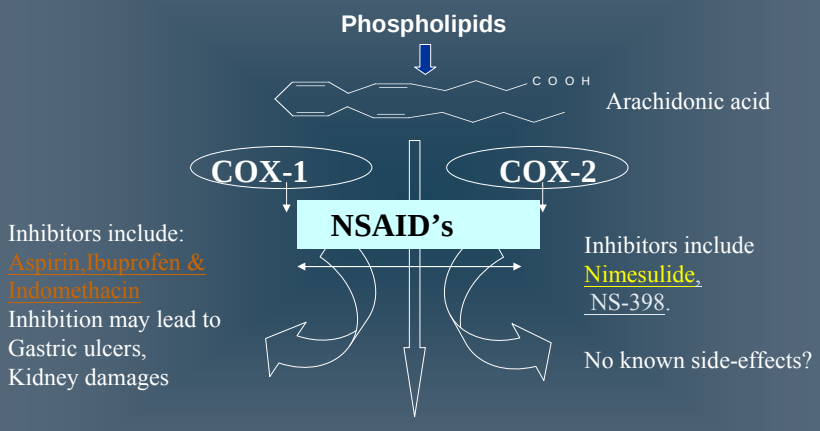
Nimesulide

- Nimesulide is rapidly and extensively absorbed in its oral form (tablets, granules or suspension) and it has a relatively short half-life(1.56 to 4.95 hr) in humans. This could account for the relatively fewer cases of severe gastrointestinal and renal toxicity reported.
- Nimesulide is mainly eliminated by metabolic transformation, via the cytochrome-P450 system, in the liver. Its principal metabolite is the 4'-hydroxy derivative. Excretion of the unchanged drug in the urine and faeces is negligible.

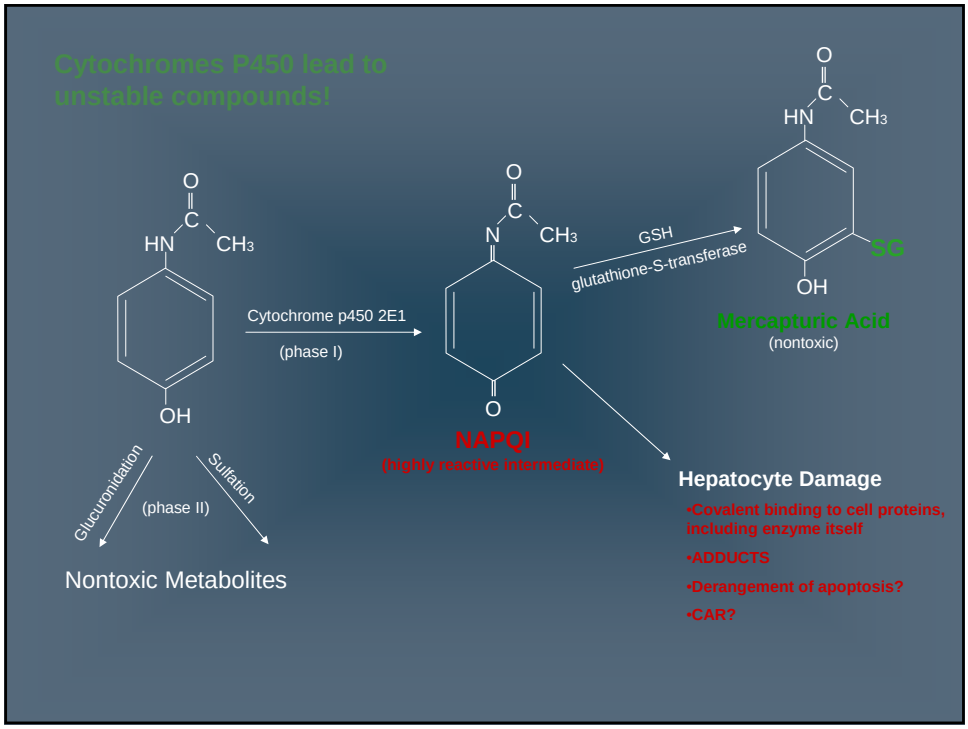
Nimesulide

- Nimesulide has been linked to various cases of acute hepatitis, especially in women.
- Onset of symptoms varies between one and 15 weeks after ingestion, although a delay of up to eight months has been reported in one case report.
- Centrilobular or bridging necrosis and, occasionally, bland cholestasis have been reported on liver histology.
- Hypersensitivity features with peripheral eosinophilia have been reported, especially early during the onset of liver injury.
- Unfortunately, detailed and informed mechanistic studies are lacking.

Free radicals trigger the synthesis of Prostaglandins and Prostacyclins.



Pain is caused by the effects of these prostaglandins which are released in the inflammatory process.



The Anti-Inflammatory Drug, Nimesulide (4-Nitro-2-phenoxymethane-sulfoanilide), Uncouples Mitochondria and Induces Mitochondrial Permeability Transition in Human Hepatoma Cells: Protection by Albumin

The American Society for Pharmacology and Experimental Therapeutics
104125/3121413

JPET 318:444–454, 2006

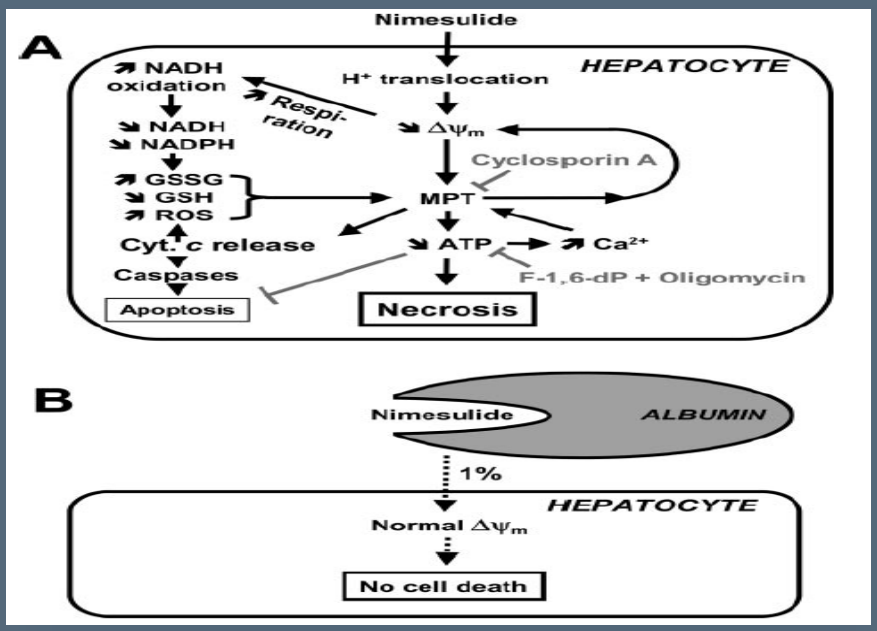


Fig. 8. Suggested effects of nimesulide in HUH-7 cells.

Conclusion


THANK U