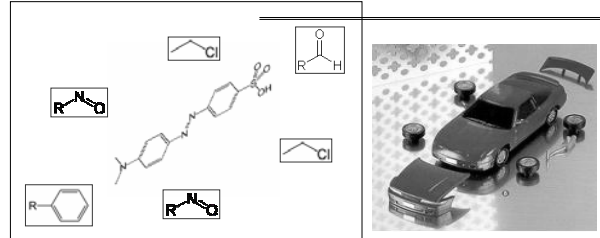


Drug Analogues – An Under-recognized Threat to the Society

Dr WT Poon
MSc, MRCP(UK), FHKAM(Pathology)
HA Toxicology Reference Lab

What is drug analogue?

- **Drug analogue** is created by modifying the chemical structure of existing drugs

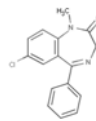


What is it for?

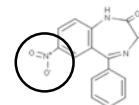
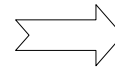
- Strategy used by drug companies
- To find **new** drugs with similar pharmacology as the parent drug



Like Father, Like Son



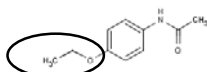
Diazepam



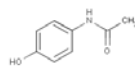
Nitrazepam

Similar structure \neq Similar pharmacology

- Drugs with similar structures may not share similar efficacy / toxicity



Phenacetin



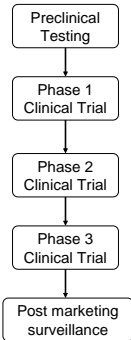
Paracetamol
(PANADOL)

withdrawn in 1980 due to
carcinogenicity & renal toxicity

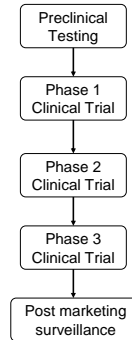
- It is prudent to test the **safety & efficacy** before a new drug analogue is marketed for human use



Drug testing process

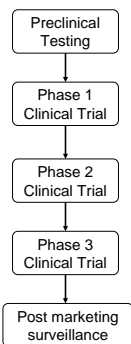


Drug testing process



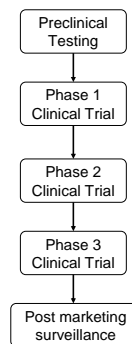
- Perform **cell-culture and animal experiments** to obtain safety data:
 - Toxicity
 - Carcinogenicity
 - Teratogenicity

Drug testing process



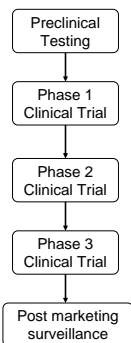
- Small no. healthy volunteers
- Small dosage
- To obtain information about:
 - drug absorption and metabolism
 - effects on organs and tissues
 - dose related side effects

Drug testing process



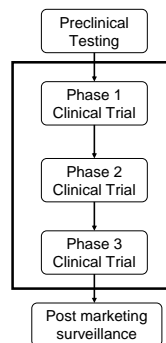
- Several hundred health-impaired patients
- To find out effectiveness of the drug in treating disease

Drug testing process



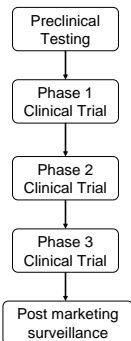
- Involves thousands of health-impaired patients
- Treatment and control arms
- To assess efficacy and risk-benefit ratio

Drug testing process



- Clinical trials prior to marketing only identify **common** adverse effects ($\geq 1:250$)

Drug testing process



- Detect **rare or long-term adverse effects** over a much larger patient population and timescale than was possible during the initial clinical trials
- Such adverse effects may result in the **withdrawal or restriction** of a drug

Vioxx (Rofecoxib)

- approved by the FDA in 1999
- In Sep 2004, drug company voluntarily withdrew it because of reports of heart attack and stroke associated with long-term, high-dosage use



Drug testing is lengthy & costly

- On average, it costs US\$ 1 billion to bring a new drug to market
- Phase 3 clinical trials are the most expensive and time-consuming part of the process
- Phase 3 clinical trials are often conducted in different countries, which can be a challenge for regulatory approval
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Why All The Trouble??

Thalidomide disaster



Illicit drug analogue

- Illicit drug analogues are marketed for human consumption **without** the above-mentioned testing process

What is the risk?

- Have not undergone **formal testing** - potential adverse effects are numerous & unpredictable

ALL users would become guinea pigs!!



N-nitroso-fenfluramine

- If N-nitrosofenfluramine were an investigational drug for formal evaluation, it would have been abandoned already



- M/28, good past health
- Unsteady gait X 1 week
- Fell several times

- P/E
 - Failed heel-toe walking
 - Tend to fall
 - No other cerebellar signs
- CT brain: Normal

- “Malaise”
- Took herbal pill 8 days before admission
 - From convenient store
 - Recommended by friend
- Drug induced ataxia suspected

Herbal pill

- Claimed for male erectile dysfunction
- Labeled to contain herbal ingredients only
- “不含普多芬”

昔多芬

- 昔多芬 = Sildenafil
- For male erectile dysfunction
- Phosphodiesterase (type 5) inhibitor → cGMP ↑ → vasodilation → erection
- Side effects:
 - headache, dyspepsia, flushing, myalgia, rhinitis
- NO ataxia

Laboratory findings

- No sildenafil detected
- However, **acetildenafil** was detected !!

Acetildenafil

- NOT a marketed drug !!
- Illicit drug analogue of sildenafil



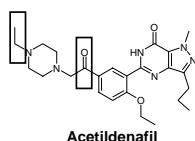
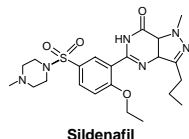
- Share similar pharmacology as sildenafil?
- May not be so...
 - The patient deny erectile dysfunction BEFORE taking the herbal pill
 - But he had erectile dysfunction AFTER !!!

Any adverse effects associated with acetildenafil reported?

- No report in literature
- Does **NOT** mean no adverse effects !!
 - No formal testing done
 - As a concealed ingredient, no post-marketing surveillance

Ataxia related?

- Sildenafil is highly specific for PDE type 5
- Structure of acetildenafil is modified and may lead to:
 - loss of PDE5 specificity
 - inhibit other PDEs



Human distribution of PDEs

Isoenzyme family	Substrate specificity	Tissue distribution
PDE1	cAMP	Brain, lung, heart
PDE2	cAMP/cGMP	Brain, adrenal cortex, liver, goblet cell
PDE3	cAMP	Smooth muscle, platelets, cardiac muscle
PDE4	cAMP	Very wide tissue distribution
PDE5	cGMP	Very wide tissue distribution: PDE5A1: kidney, bladder, prostate, urethra, PDE5A3: heart, bladder, prostate, u
PDE6	cGMP	Retina (rods and cones)
PDE7	cAMP	Skeletal muscle, T-lymphocytes
PDE8	cAMP	Testis, ovary, gastrointestinal tract
PDE9	cGMP	Spleen, gastrointestinal tract, brain
PDE10	cAMP/cGMP	Brain, testis, thyroid
PDE11	cAMP/cGMP	Smooth muscle; cardiac muscle; prostatic glands; testis; liver; kidney; skeletal

Carson CC, Lue TF. Phosphodiesterase type 5 inhibitors for erectile dysfunction. BJU Int. 2005;96(3):257-80.

Adverse effects of Acetildenafil?

- NO one knows !!
- Need formal animal and human studies
- Before that, the drug analogue should not be allowed for use in humans

Illicit analogue problem in H.K.

- Limited market survey
- male erectile dysfunction health products available in Hong Kong
- Twenty products were bought over the counter
- Claim 100% herbal
- Tested for erectile dysfunction drugs and analogues

Results

- 1 was found to contain sildenafil
- 10 contain illicit drug analogues:
 - Acetildenafil (Sildenafil analogue)
 - Hydroxy acetildenafil (Sildenafil analogue)
 - Hydroxy homo sildenafil (Sildenafil analogue)
 - Piperidenafil (Vardenafil analogue)



The story did not end...

- Product similar to the one taken by patient was available in some stores and on internet

"Do not contain acetildenafil!"

Laboratory Findings:

- **NO acetildenafil / sildenafil was found**
- **Piperidenafil was detected !!**

Legal loophole

- The H.K. Pharmacy and Poisons Ordinance only provides control on adulteration of health products with registered drugs
- These illicit drug analogues are **NOT** regarded as "drugs"
- Their use in health products is therefore not under legal regulation

Summary

- Problem of illicit drug analogue is **huge**:
 - Slimming agent
 - Male erectile dysfunction product
 - Others ...
- Adverse effects are largely **unpredictable**
- Their use is not under legal regulation

How to control the problem?

- In Hong Kong, drugs of abuse are banned based on chemical structure only
- If a chemical is similar in structure to an already banned drug, it too is banned. E.g. ecstasy
- **The same principle could apply to illicit analogues of other drug classes**

Acknowledgements

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