

Anti-hyperglycaemic Therapies

Comparative Safety

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Type 2 diabetes at the Newcastle Diabetes Centre

- **Around 4000 patients under care**
 - **2830 on Annual Review database for 1998**
 - **Diet-alone 680 (24)**
 - **Sulphonylurea 948 (33)**
 - **Metformin 711 (25)**
 - **Insulin 922 (33)**
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n (%)

Clinical Management of Type 2 Diabetes

- **Serious condition**
 - **Treatment required and effective**
 - **Limited number of treatment options**
 - **All options have potential for adverse effects**
 - **Treatment benefits exceed risk**
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Serious Adverse Effect Profiles of Anti-hyperglycaemic Drugs

	Disabling hypoglycaemia	Lactic acidosis	Acute hepatic injury
Sulphonylureas	+	-	-
Metformin	-	+	-
Troglitazone	-	-	+
Insulin	+	-	-

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Metformin

- **Recently approved (USA)**
 - **Similar exposure to troglitazone**
 - **Well characterized adverse event profile**
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Metformin – Serious Adverse Events

US Post-marketing reports

- **First year in the market**
 - **~1 million people exposed**
 - **47 cases confirmed lactic acidosis**
 - **20 deaths**
 - **Estimated event rate:**
4.7 per 100,000-pt (1/20 000)
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Misbin et al 1998.

**Metformin and troglitazone – fatal events
Comparative first-year post-marketing data**

	Metformin^a	Troglitazone^b
Dates	May 1995- Jun 1996	Mar 1997- Apr 1998
Exposure	1 000 000	1 050 885
Fatal events	20	17
Rate (per 100,000-pt)	2.0	1.7

^aMisbin et al 1998, NEJM.

^bMisbin 1999, Ann Int Med.

Metformin-related lactic acidosis
Swedish Adverse Drug Reactions Advisory Committee

Report	Campbell 1985 Berger 1985	Wiholm & Mynhed 1993	Wiholm & Mynhed 1993
Years	1972-1981	1977-1981	1987-1991
Cases	8.4	15.0	2.4
Deaths	2.4	N.D.	N.D.

Rates per 100,000-pt-yr.

N.D. = No Data

Metformin-related lactic acidosis (2)

Report	Berger & Amrein 1978	Bailey & Natrass 1998	Strang et al 1997
Years	1972-1977	1976-1986	1980-1985
Country	Switzerland	UK	Canada
Cases	6.7	2.7	18
Deaths	N.D.	N.D.	9

Rates per 100,000-pt-yr.

N.D. = No Data

Metformin-related lactic acidosis - Conclusion

Cases 2.4 – 18.0

Deaths 0.9 – 9.0

Rates per 100,000-pt-yr.

**Sulphonylurea-related severe hypoglycaemia
Swedish Adverse Drug Reactions Advisory
Committee 1972-1987**

Report	Asplund et al, 1983	Asplund et al, 1991
Analysis	Campbell, 1985	Home, 1999
Years	1971-1981	1980-1987
Drug	glyburide	glipizide
Cases (n, rate)	51, 19.0	19, 15.0
Deaths (n, rate)	10, 3.2	2, 1.6

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Hypoglycaemia on sulphonylureas Database studies

Author	Database	Definition	Rate	Death
Shorr et al 1996	Tennessee Medicaid/ Medicare	Hospital- requiring	1,230	0.8
van Staa et al 1997	UK General Practice (VAMP)	Physician- requiring	1,770	N.D.

Rate per 100,000-pt-yr, death %-cases.
N.D. = No Data

Sulphonylurea-related severe hypoglycaemia

Conclusion

Cases 1.9 – 1,770

Deaths 1.4 – 9.8

Rates per 100,000-pt-yr.

Hypoglycaemia in the UKPDS

	All (100,000-pt-yr ⁻¹)	Severe ^a (100,000-pt-yr ⁻¹)	Death (n)
Chlorpropamide	11,000	400	0
Glibenclamide	17,700	600	0
Insulin	36,500	2,300	1

^aRequiring assistance.

Insulin-related hypoglycaemic death

- **Perceived uncommon in Type 2 diabetes**
 - **UKPDS: 1 death / 1500 patients**
 - **Risk estimate too uncertain to calculate**
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Type 2 diabetes
Therapy-related severe adverse events

	Deaths
Metformin	0.8–9.0
Sulphonylureas	1.4–9.8
Insulin	(5.0–50.0)
Troglitazone	2.0

Rates per 100,000-pt-yr.

Type 2 diabetes

Rates of benefit from therapy – deaths

Deaths in Type 2 diabetes

	All (rate)	Diabetes- related (rate)	Prevented (%)	Prevented (rate)
UKPDS	1,840	1,100	-10	110.0
WESDR	6,240	3,510	N.D.	350.0

Rate per 100,000-pt-yr.

N.D. = No Data

Serious Adverse Events in Type 2 Diabetes Conclusion

- **All drug treatments for Type 2 diabetes carry some risk**
 - **The risk is low – particularly compared to benefit**
 - **Risk from troglitazone is comparable to established therapies**
 - **Troglitazone risk has decreased with time**
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Thank you for your attention

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