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Specific oral contraceptive use and venous thromboembolism resulting in hospital admission

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Abstract

Objective To determine whether there is an increased risk of venous thromboembolism (VTE) with anti-androgen oral contraceptives containing cyproterone acetate and ethinyloestradiol.

Methods Comparison of the frequency of specific oral contraceptive use in patients aged 15 to 55 years discharged from hospital with radiologically confirmed deep vein thrombosis (DVT) and/or pulmonary embolism (PE) with the expected frequency of use derived from national prescription data.

Main Outcome Measure Ratio of observed frequency of specific oral contraceptive use in patients with VTE *versus* expected frequency of use.

Results The rank order for observed versus expected use was anti-androgen > third-generation, > second-generation, > progestogen-only oral contraceptive agents with ratios of 1.93, 1.36, 0.70, and 0.39, respectively.

Conclusion The risk of VTE resulting in hospital admission associated with anti-androgen oral contraceptive use is at least as high as with third generation use.

During the last decade, the increased risk of VTE associated with different types of oral contraceptive agents has been increasingly recognised.[1] In particular, epidemiological studies have identified that women taking third-generation oral contraceptives containing either gestodene or desogestrel have a thrombotic risk about two-fold higher than that of women using second-generation oral contraceptives containing levonorgestrel.[2–5]

There is also preliminary evidence of an increased risk of VTE with the anti-androgen oral contraceptive containing cyproterone acetate and ethinyloestradiol, although the relative risk compared with other oral contraceptive agents has not been clearly determined due to the small number of cases (a total of 30 women taking anti-androgen oral contraceptive agents in the three studies).[6–8]

We have investigated this issue by comparing the frequency of use of specific oral contraceptive agents in patients discharged from hospital with a radiologically-confirmed diagnosis of DVT and/or PE with expected frequencies derived from national prescription data.

Methods

We reviewed the medical records of female patients aged between 15 and 55 years who were discharged with a diagnosis of DVT or PE between January 1996 and April 2002. Records were identified from three tertiary referral hospitals (Wellington, Green Lane, and Auckland) and three district general hospitals (Hutt, Kenepuru, and Masterton) in New Zealand.

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Inclusion criteria were:

- A primary or secondary discharge diagnosis of DVT or PE, and
- Radiographic confirmation by at least one of a positive venous compression Doppler ultrasound, positive venography, a high or intermediate probability ventilation/perfusion scan, positive helical computed tomography (CT) with pulmonary angiography, or pulmonary angiography; or
- Confirmation by post mortem examination.

Information was abstracted from the medical records, including documented current oral contraceptive use, which was classified according to five categories: progestogen only, second generation, third generation, anti-androgen, and brand not specified. The two anti-androgen agents were Diane-35 and Estelle-35, both containing 2 mg cyproterone acetate and 35 mcg ethinyloestradiol.

The expected frequency of use of each of the five categories of oral contraceptive agents was determined from national prescription records for each year 1996 to 2002, held by the New Zealand Pharmaceutical Management Agency (PHARMAC).

A Chi-squared test was performed comparing the observed numbers of subjects with DVT and/or PE for each category of oral contraceptive compared to what would be expected based on national prescribing.

Results

There were 330 subjects, with a median (range) age of 40 (15 to 55) years included in the analysis. The diagnosis was DVT alone in 179 (54.2%), PE alone in 102 (30.9%), and both DVT and PE in 49 (14.8%). In 81 of the 95 (85%) subjects for whom oral contraceptive therapy was recorded, the specific brand of the agent was stated (Table 1).

Table 1. Comparison of the observed frequency of specific oral contraceptive use in patients with VTE discharges from hospital versus expected frequency of use derived from national prescription data

Type of oral contraceptive	Observed frequency N (%)	Expected frequency N (%)	Observed/ expected
Progestogen only pill*	4 (5%)	10.4 (13%)	0.39
Second-generation oral contraceptive†	25 (31%)	35.6 (44%)	0.70
Third-generation oral contraceptive‡	37 (46%)	27.2 (34%)	1.36
Anti-androgen§	15 (19%)	7.8 (10%)	1.93

*Ethynodiol diacetate or levonorgestrel or norethisterone; †Ethinyloestradiol + levonorgestrel or norethisterone Mestranol + norethisterone; ‡Ethinyloestradiol + desogestrel or gestodene; §Ethinyloestradiol + cyproterone acetate; VTE=venous thromboembolism.

The observed frequencies were different from the expected frequencies, with progestogen only and second-generation agents less frequently used in subjects with VTE than expected, and third-generation and anti-androgen agents more frequently

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used than expected (Chi-squared statistic 17.36, df 3, p=0.0006). The two main contributions to the Chi-squared statistic were the lower than expected use of progestogen only (Chi-squared contribution 4.0) and the higher than expected use of anti-androgen agents (Chi-squared contribution 6.7).

The relative market share of the different oral contraceptive agents varied throughout the study period, primarily in response to the public concerns raised regarding the risk of VTE associated with third generation oral contraceptive use. This resulted in a marked reduction in the market share of third generation agents from 1999, with a corresponding increase in the other agents; in particular, second generation agents (Table 2).

Table 2. National market share for specific oral contraceptive agents during the period of the study

Year	Type of oral contraceptive pill (OCP) sold in New Zealand (%)			
	POP	2nd Generation	3rd Generation	Anti-androgen
1996	10.6	23.4	59.1	6.9
1997	10.8	27.8	53.5	7.9
1998	11.4	29.9	50.7	8.0
1999	14.1	50.5	26.7	8.8
2000	14.3	55.2	19.4	11.0
2001	14.1	57.3	16.1	12.4
2002	14.0	58.4	14.4	13.1

POP=progestogen only pill: ethynodiol diacetate or levonorgestrel or norethisterone;
2nd Generation=ethinyloestradiol + levonorgestrel or norethisterone/norethisterone + mestranol;
3rd Generation=ethinyloestradiol + desogestrel or gestodene;
Anti-androgen=ethinyloestradiol + cyproterone acetate.

The rank order of the observed versus expected frequency of specific oral contraceptive use was maintained in the periods before and after 1999, with ratios for anti-androgen, third-generation, second-generation, and progestogen-only agents of 1.21, 1.05, 1.01, 0.57 and 2.27, 1.88, 0.60, 0.29 for the periods 1996 to 1998 and 1999 to 2002, respectively.

Discussion

Principal findings

This study has identified a greater than expected use of anti-androgen oral contraceptive agents in women with VTE resulting in hospital admission. This disproportionately greater use of anti-androgen agents was observed throughout the 6-year period of the study, and was at least as high as with the third-generation oral contraceptive agents.

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Methodological issues

There are a number of methodological issues which are relevant to the interpretation of the study findings. One possible confounder is indication, if anti-androgen agents were preferentially prescribed to women who were perceived to be at higher risk of VTE. However, the available evidence indicates this is unlikely, as this contraceptive agent is registered and marketed primarily for its anti-androgen properties and not for any reduced thrombotic risk. In addition, the proportion of prescriptions for anti-androgen agents increased from 1999, in contrast to a marked fall with the third-generation contraceptive agents coinciding with concerns over their VTE risk.

However, it is possible that anti-androgen use may have been associated with obesity, due to its indication for women with polycystic ovary disease. As obesity increases the risk of VTE,[9] this could have led to an over-estimation of the risk of anti-androgen agents. Conversely, on the basis of their indication for acne, anti-androgen agents may have been preferentially prescribed to younger women, which would have resulted in an under-estimation of their risk.

The publicity in 1999 relating to the risk of third-generation oral contraceptive agents could have led to potential biases which operated in opposite directions. These biases could have occurred if women at high risk were less likely to be prescribed third-generation agents, or if women taking third-generation oral contraceptives were more likely to be referred and diagnosed as having VTE.

A major effect of these biases was not evident from the time trend data, in which the rank order for the specific oral contraceptive agents was maintained prior to and after 1999, when the major publicity about the risks of third-generation agents and associated reduction in market share occurred. Finally, another source of potential bias relates to the 14 subjects in whom the specific brands of oral contraceptive therapy was not stated.

Comparison with other studies

The findings complement the three previous epidemiological studies that have investigated the relative use of VTE in subjects using anti-androgen agents. The World Health Organization (WHO) study identified a 15-fold risk of VTE with the anti-androgen product containing cyproterone and ethinyloestradiol at a dose of 35 mcg compared with non-users.[6]

Compared with non-users, a four-fold greater risk of VTE was reported with anti-androgen products containing cyproterone and the higher 50 mcg dose of ethinyloestradiol. This paradox, of a higher risk associated with a lower oestrogen dose has also been observed with desogestrel[6] and requires further investigation.

The case-control study based on the United Kingdom General Practice Research Database reported that the relative risk of VTE with anti-androgen oral contraceptive agents was four times greater than those using second-generation oral contraceptive agents.[7] An absolute 13.3-fold increased risk was identified with anti-androgen oral contraceptive agents from this study, similar to the 17.6-fold estimate reported in the New Zealand case-control study of fatal PE.[8]

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Clinical implications:

Our findings raise several concerns. For example, we need better methods to assess the potential risk of VTE before introducing novel oral contraceptive agents into clinical practice. This is illustrated by the recent report of VTE associated with the novel oral contraceptive ethinyloestradiol with drospirenone.[10]

Furthermore, prolonged post-marketing surveillance and epidemiological studies are needed to investigate the occurrence of VTE following their introduction and widespread use. VTE is an uncommon event in young women, and clinical trials of hormonal contraceptives are likely to have insufficient statistical power to detect infrequent events, particularly if subjects recruited are appropriately screened for risk of VTE.

Another concern is the inadequate assessment of risk of VTE in our patient group, with 9.3% of women on second- or third-generation oral contraceptive agents despite a past history of VTE. Furthermore, despite a reduction in the overall use of third-generation-combined oral contraceptive agents since the extensive publicity of their risk of VTE, they maintain a significant market share.

Reassuringly, oral progestogen-only contraceptives were prescribed less frequently than expected in women who were admitted to hospital with a VTE. It should be acknowledged that this finding does not indicate that progestogen-only preparations do not increase the risk of VTE, rather than the risk is higher with other types of hormonal contraceptive agents. However it does support the current recommendation that women at high risk of VTE should preferentially be prescribed either a progesterone-only pill or non-hormonal measures.[11,12]

In summary, these findings indicate an increased risk of VTE resulting in hospital admission with the use of anti-androgen oral contraceptive agents containing cyproterone and ethinyloestradiol. They also reinforce the importance of assessing the risk of VTE in women in whom oral contraceptive agents are considered.[1,9,11]

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