Parenteral oestrogens for prostate cancer: a systematic review of clinical effectiveness and dose response

Centre for Reviews and Dissemination

CRD summary
This CRD-conducted review concluded there was insufficient evidence to make definitive conclusions about parenteral (non-oral) oestrogen safety and efficacy in prostate cancer treatment because of the varied and low-quality studies available. However, there was some evidence that combined parenteral and oral oestrogens increased cardiovascular mortality and morbidity. Further research into parenteral oestrogens (but not combination therapies) for prostate cancer was recommended.

Objectives
To assess the effectiveness and safety of parenteral (administered by other routes than through the digestive tract) oestrogen in the treatment of prostate cancer, and to examine any dose relationship.

Review methods
A wide range of databases (including MEDLINE, EMBASE and DARE) and other Internet resources were searched for published and unpublished studies with no language restrictions. Randomised controlled trials (RCTs) of parenteral oestrogen in patients with prostate cancer were eligible for inclusion; other study designs were also included to examine dose/response.

Study selection, data extraction and study quality assessment were performed by one reviewer and independently checked by another. Data were tabulated and summarised in a narrative synthesis.

Results of the review
Twenty-two studies were included in the review comprising 17 RCTs (3,627 patients; range 30 to 917) assessing the effectiveness and safety of parenteral oestrogens, and three studies (82 patients; range 17 to 38) examining dose relationships. Most studies were not reported in sufficient detail to allow full assessment of their methodological quality, but were mainly of poor quality or were poorly reported.

The included studies differed in types of parenteral oestrogens (most assessed intramuscular polyoestradiol phosphate), doses administered, patients’ characteristics (disease status, prior treatments and risk of cardiovascular system morbidity/mortality), outcome measures reported, comparators used, and duration of follow-up. None of the included studies reported long-term serious adverse events (such as osteoporosis) in any detail. The largest and highest quality trials did not provide long-term survival data.

Low-dose intramuscular oestrogen (polyoestradiol phosphate 160mg/month) at levels not sufficient to produce castrate levels of testosterone may not be as effective as orchidectomy (testes removal) or luteinising-hormone releasing hormone treatment in controlling prostate cancer measured by tumour response. Overall survival appeared comparable between these groups.

High-dose intramuscular oestrogen (polyoestradiol phosphate 240mg/month) at levels sufficient to produce castrate levels of testosterone may be as effective as orchidectomy and LHRH in controlling prostate cancer measured by disease-free and overall survival.

Intramuscular polyoestradiol phosphate use (at 160mg and 240mg) appeared to be associated with increased cardiovascular morbidity compared with conventional hormonal treatments for prostate cancer, but the level of cardiovascular morbidity was lower than that previously seen with oral oestrogen.
There was no evidence of differences between intramuscular polyoestradiol phosphate and conventional hormone therapy for cardiovascular mortality. The disparity between cardiovascular morbidity and mortality might be real, or it might be because the mortality data were relatively sparse or because of the relatively short follow-up on most of the studies.

Combination therapy of Intramuscular polyoestradiol phosphate (80mg/month) plus oral oestrogen appeared to be as effective as comparison treatments (orchidectomy, estramustine phosphate or radiotherapy) in controlling prostate cancer. However, the levels of cardiovascular mortality and morbidity were higher for combination oestrogen treatment than for the comparator treatments.

**Conclusions**
There was insufficient evidence to draw definitive conclusions on the safety and efficacy of on the use of parenteral oestrogen in prostate cancer because of the differences between studies and their low methodological quality. The available evidence on combined parenteral and oral oestrogens suggested that cardiovascular mortality and morbidity may be considerably elevated by their use. Further well-conducted trials of parenteral oestrogen (but not combination therapies) as an alternative to existing hormone treatments were recommended.

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This is a high quality systematic review involving CRD that meets the criteria for inclusion on DARE. As CRD reviews are of high quality a structured abstract will be written presenting a brief summary of the review methods, the results and conclusions.